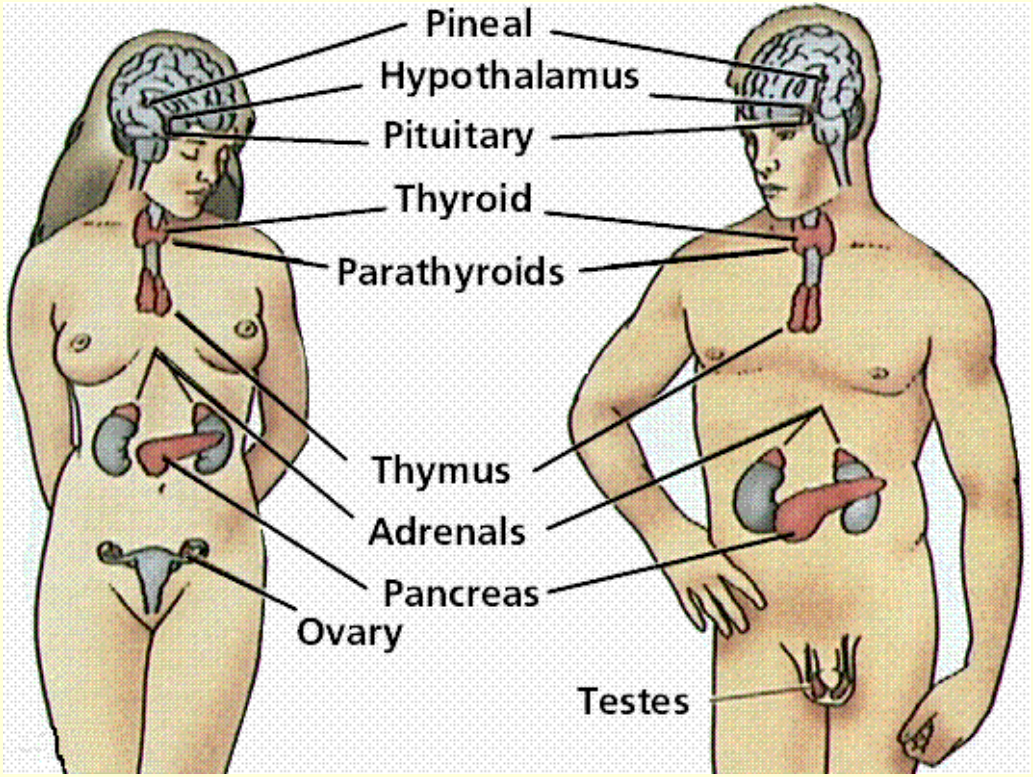
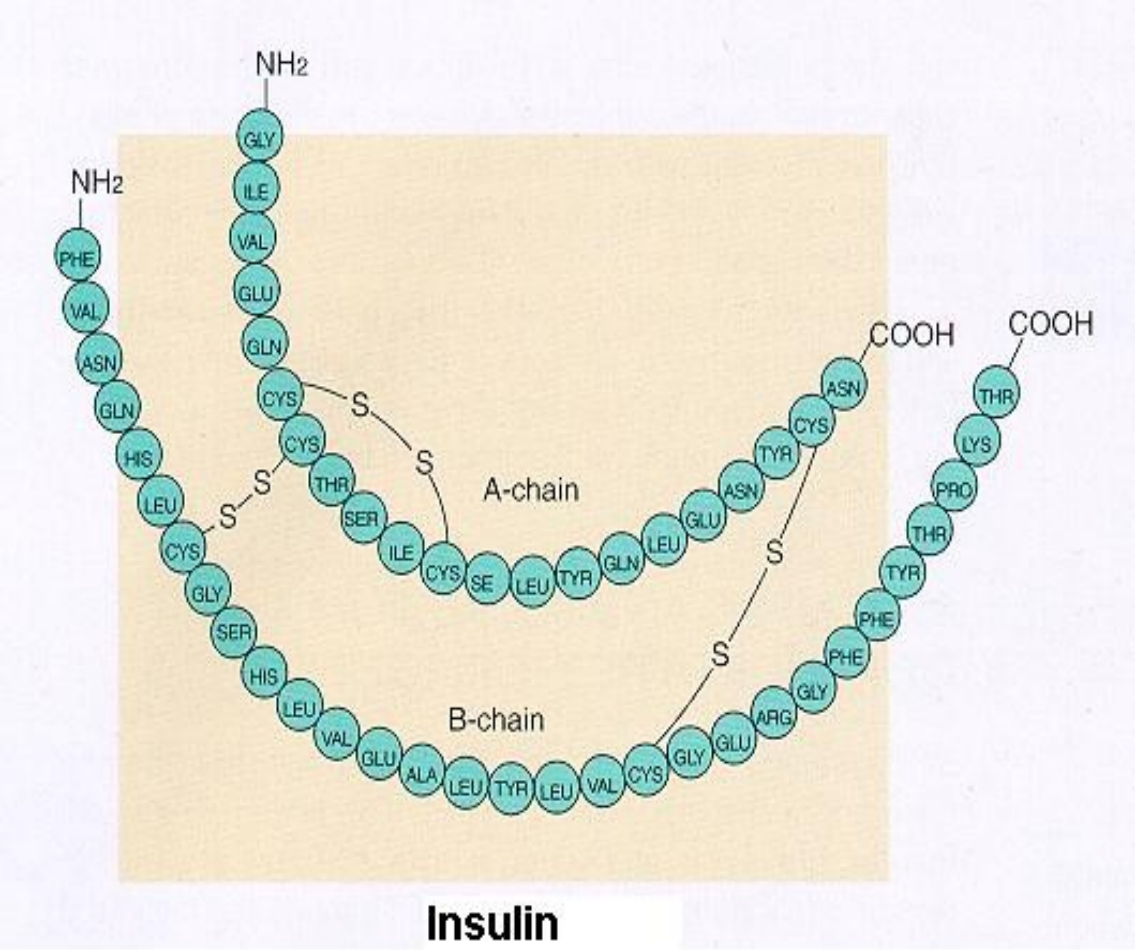
ENDOCRINE SYSTEM PHYSIOLOGY



HORMONE

The term ***hormone*** is derived from Greek verb which means to excite



Insulin

TYPES OF SECRETION

- **Endocrine secretion** – substance released by cell into blood stream that affects distant cells.
- **Exocrine secretion** – substance released by cell into a duct that leads to epithelial surface (on to skin or into gut). Action doesn't depend on receptors in target tissue.

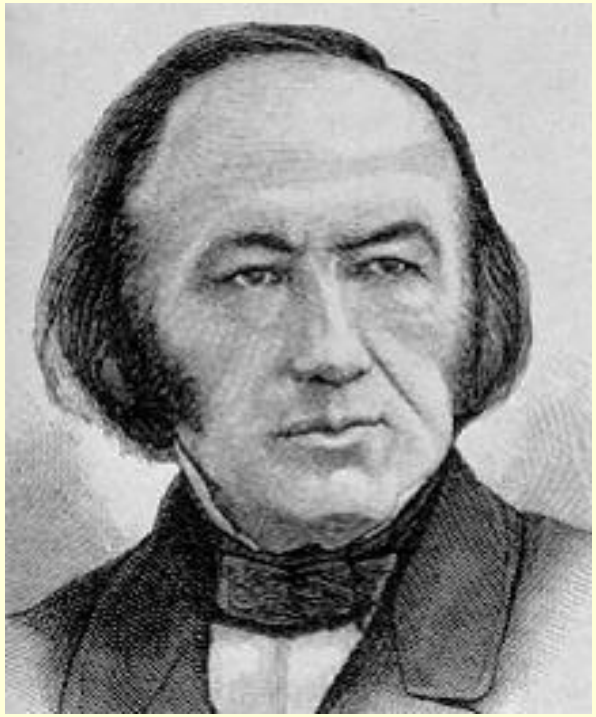
Arnold A. Berthold (1803-1861)

In one of the first endocrine experiments ever recorded, Professor Arnold A. Berthold of Gottingen did a series of tests on roosters in 1849 while he was curator of the local zoo.

ABLATION AND REPLACEMENT

- Berthold found that a rooster's comb is an androgen-dependent structure.
- Following castration, the comb atrophies, aggressive male behavior disappears, and interest in the hens is lost.
- Importantly, Berthold also found that these castration-induced changes could be reversed by administration of a crude testicular extract (or prevented by transplantation of the testes).

Claude Bernard (1813-1878)



- Claude Bernard stated that the endocrine system regulates the internal environment of an animal.
- The “internal secretions” were liberated by one part of the body, traveled via the bloodstream to distant targets cells (1854).

Starling – Bayliss – Vernay

- Besides "his" law of the heart, Ernest Henry Starling discovered the functional significance of serum proteins.
- In 1902 along with Bayliss he demonstrated that secretin stimulates pancreatic secretion.
- In 1924 along with E. B. Vernay he demonstrated the reabsorption of water by the tubules of the kidney. He was the first to use the term *hormone.*

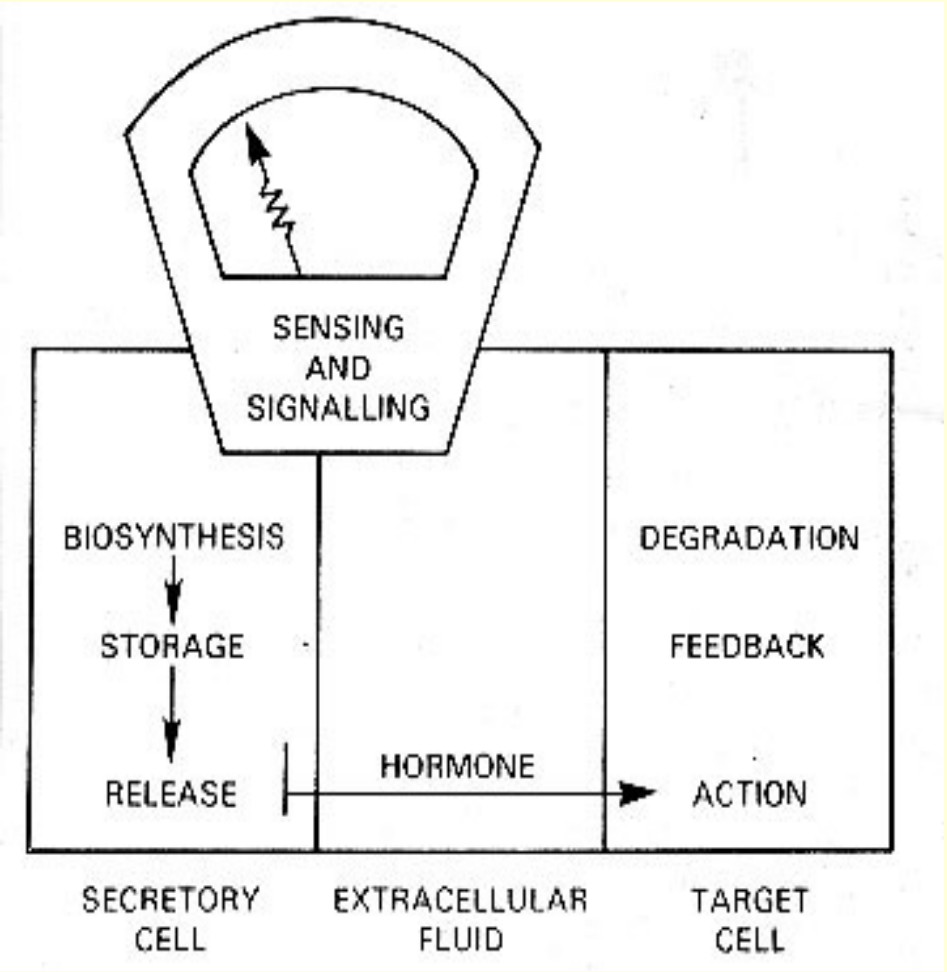
ENDOCRINE SYSTEM MAINTAINS HOMEOSTASIS

- **The concept that hormones acting on distant target cells to maintain the stability of the internal environment was a major advance in physiological understanding.**
- **The secretion of the hormone was evoked by a change in the environment and the resulting action on the target cell restored the internal environment to normal. The desired return to the *status quo* results in the maintenance of homeostasis.**

ENDOCRINE SYSTEM MAINTAINS HOMEOSTASIS

- Homeostasis — maintenance of body conditions in a stable steady state (specific conditions to survive and function of the body cells).
- Some of the body parameters kept in a steady state:
  - body temperature: regulated close to 37 deg C
  - blood pH: kept at 7.4
  - arterial blood pressure: maintained around 120/80 mm Hg
- Failure of homeostasis causes diseases and sometimes death.

SENSING AND SIGNALING

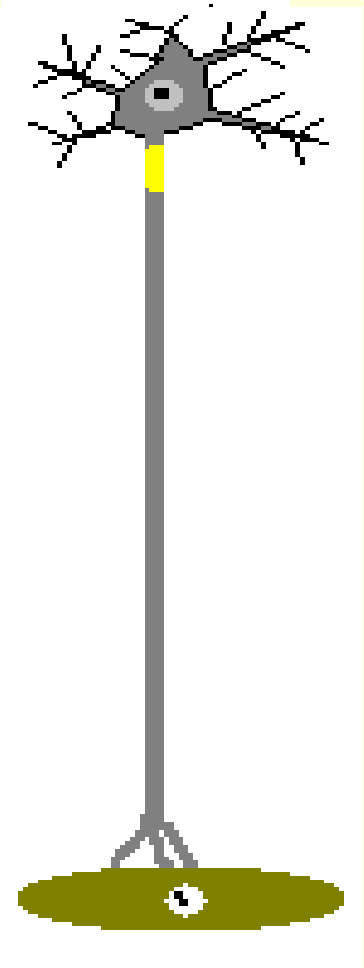


Endocrine "glands" synthesize and store hormones. These glands have a sensing and signaling system which regulate the duration and magnitude of hormone release via feedback from the target cell.

ENDOCRINE AND NERVOUS SYSTEM

- major communication systems in the body
- integrate stimuli and responses to changes in external and internal environment
- both are crucial to coordinated functions of highly differentiated cells, tissues and organs
- unlike the nervous system, the endocrine system is anatomically discontinuous

NERVOUS SYSTEM



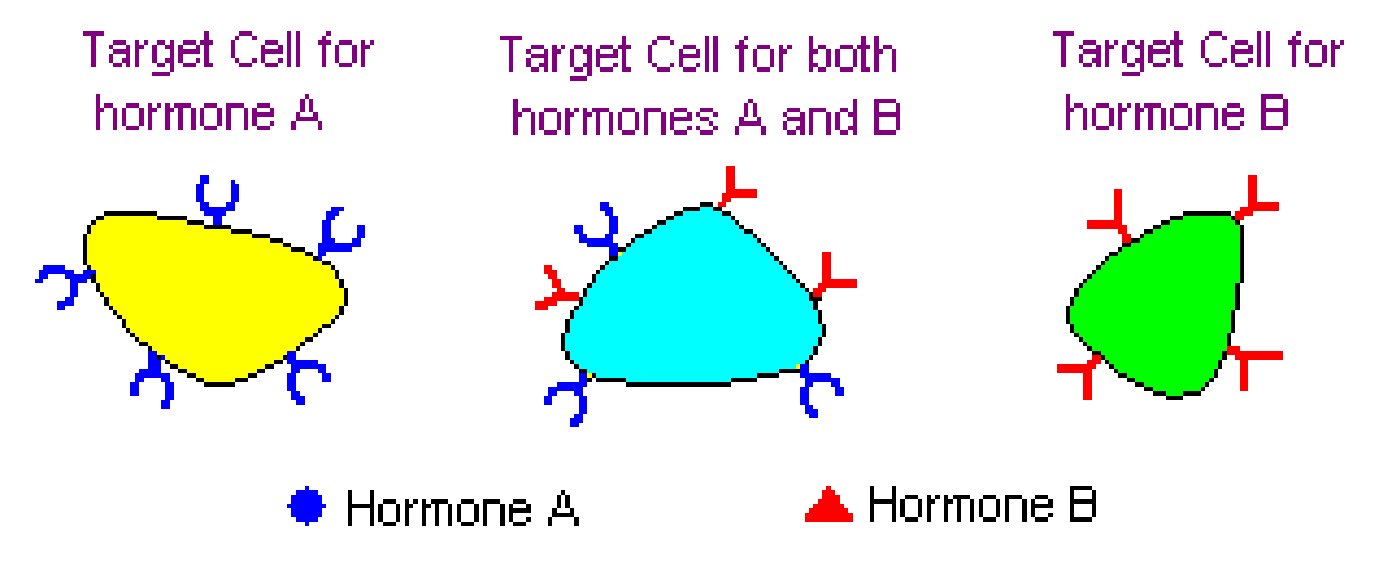
- The nervous system exerts point-to-point control through nerves, similar to sending messages by conventional telephone.
- Nervous control is electrical in nature and fast.

ENDOCRINE SYSTEM

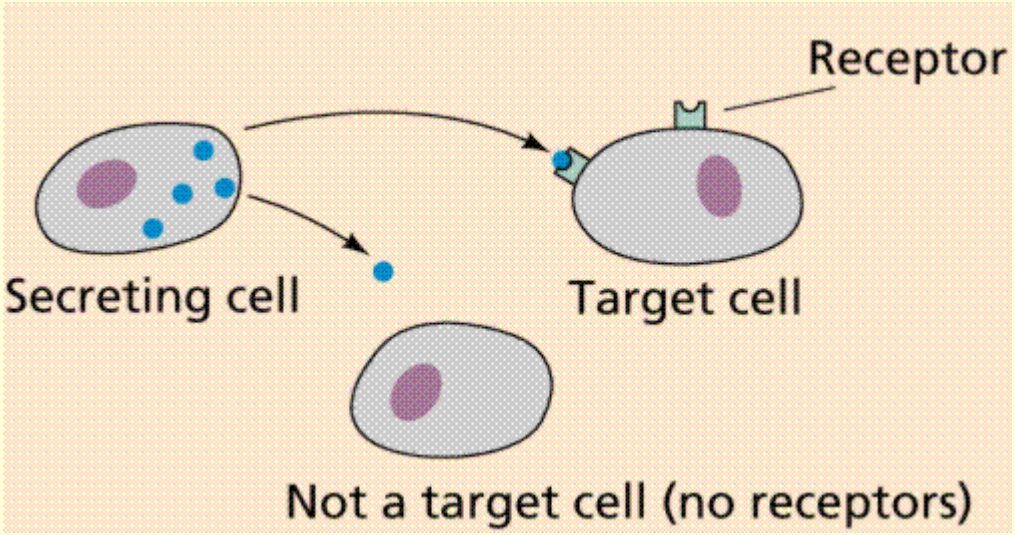
- The endocrine system broadcasts its hormonal messages to essentially all cells by secretion into blood and extracellular fluid.
- In the case of endocrine messages, cells must bear a receptor for the hormone being broadcast in order to respond.

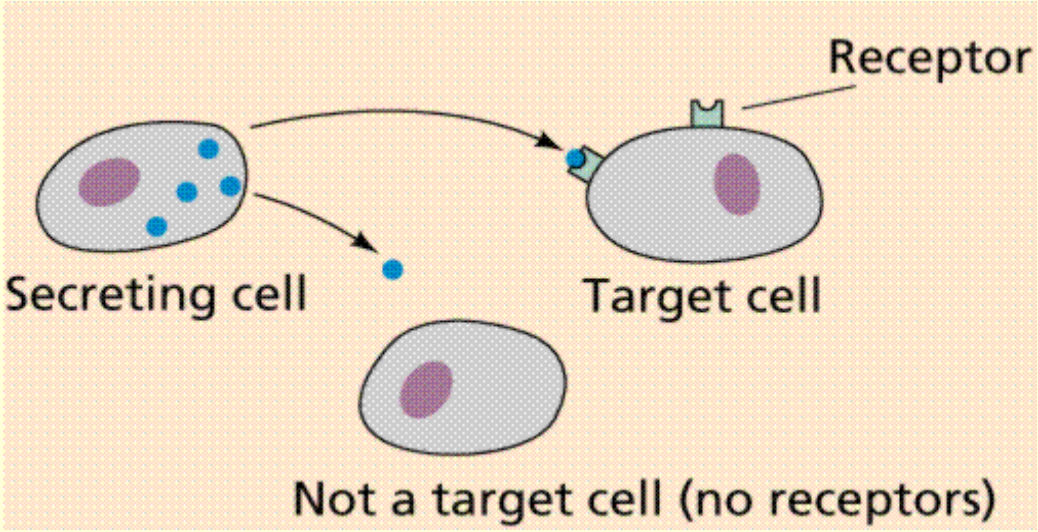
TARGET CELL HAS A SPECIFIC HORMONE RECEPTOR

Most hormones circulate in blood, coming into contact with essentially all cells. However, a given hormone usually affects only a limited number of cells, which are called target cells. A target cell responds to a hormone because it bears receptors for the hormone.



The endocrine system establishes as adequate hormone concentration at the level of receptors on target cells





MAIN FUNCTIONS OF THE ENDOCRINE SYSTEM

- maintenance of the internal environment in the body (maintaining the optimum biochemical environment)
- integration and regulation of growth and development
- control, maintenance and instigation of sexual reproduction (gametogenesis, coitus, fertilization, fetal growth and development and nourishment of the newborn)

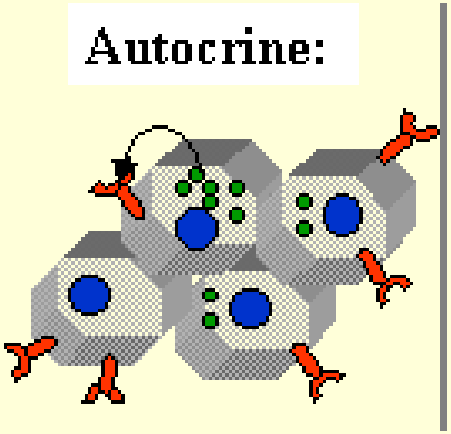
CELLS AND HORMONES

- Stimulate cell function (e.g. insulin stimulates glucose uptake)
- Inhibit cell function (e.g. somatostatin inhibits Growth hormone secretion)
- Maintain status quo (e.g. maintain blood calcium level)
- Stimulate or inhibit cell division (growth or renewal of tissues or organs)
- Stimulate cell differentiation
- Stimulate “programmed cell death” or protect cells from this process (apoptosis)

TYPES OF CELL-TO-CELL SIGNALING

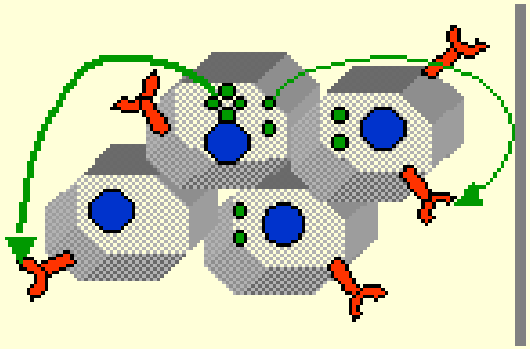
Endocrine action: the hormone is distributed in blood and binds to distant target cells.
Paracrine action: the hormone acts locally by diffusing from its source to target cells in the neighborhood.
Autocrine action: the hormone acts on the same cell that produced it.
Intracrine action: the hormone acts within the cell that produces them.

Autocrine:



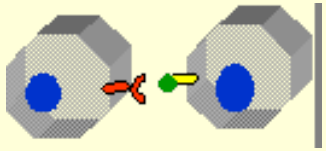
Cell produces hormone that stimulates or inhibits itself

Paracrine



Cell produces hormone that stimulates or inhibits its neighbor

Juxtacrine:

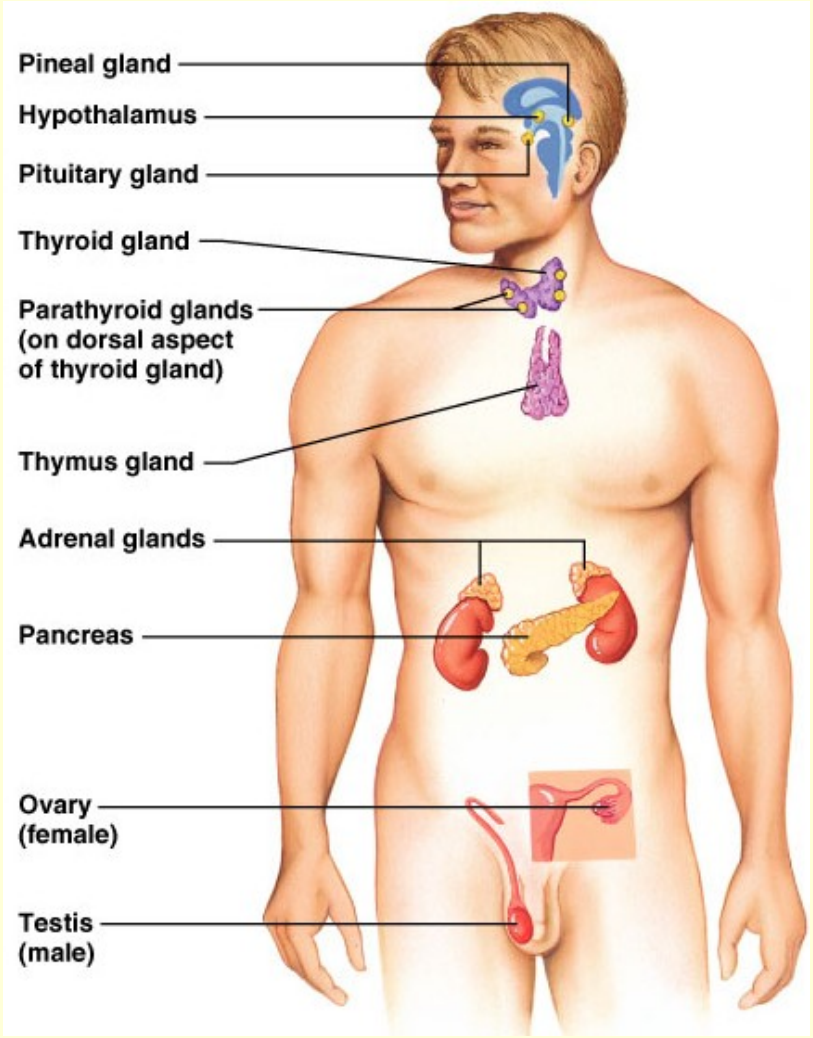


Cells sit side by side.
One has hormone on surface, the other has the receptor.

TOP DOWN ORGANIZATION OF ENDOCRINE SYSTEM

EXAMPLE:

Hypothalamus produces releasing factors that stimulate production of anterior pituitary hormone which act on peripheral endocrine gland to stimulate release of third hormone.



TYPES OF HORMONES

- Hormones are categorized into four structural groups, with members of each group having many properties in common:
  - Peptides and proteins
  - Amino acid derivatives
  - Steroids
  - Eicosanoids (fatty acid derivatives)

PEPTIDE / PROTEIN HORMONES

- Range from 3 amino acids to hundreds of amino acids in size.
- Often produced as larger molecular weight precursors that are proteolytically cleaved to the active form of the hormone.
- Peptide/protein hormones are water soluble.

Comprise the largest number of hormones (thousands)

PEPTIDE / PROTEIN HORMONES

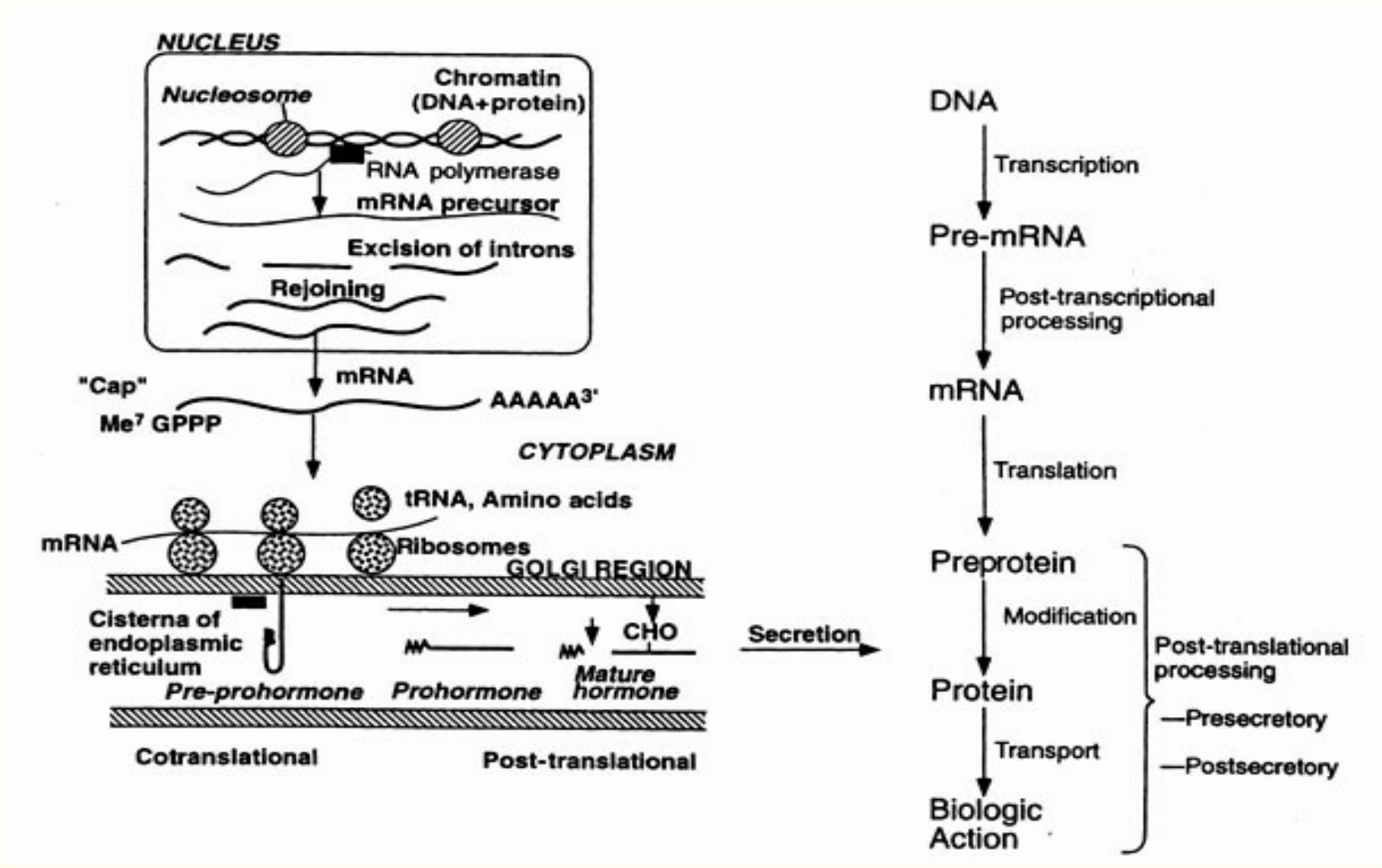
- They are encoded by a specific gene which is transcribed into mRNA and translated into a protein precursor called a preprohormone
- Preprohormones contain signal peptides (hydrophobic amino acids) which targets them to the golgi where signal sequence is removed to form prohormone
- Prohormone is processed into active hormone and packaged into secretory vesicles

PEPTIDE / PROTEIN HORMONES

- Secretory vesicles move to plasma membrane where they await a signal. Then they are exocytosed and secreted into blood stream
- In some cases the prohormone is secreted and converted in the extracellular fluid into the active hormone:

  example – angiotensin is secreted by liver and converted into active form by enzymes secreted by kidney and lung

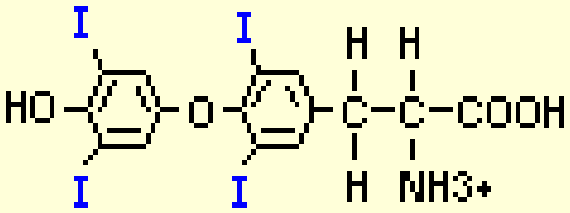
PEPTIDE / PROTEIN HORMONE SYNTHESIS



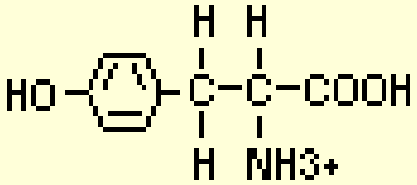
AMINO ACID DERIVATIVES

There are two groups of hormones derived from the amino acid tyrosine:

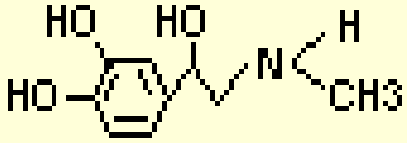
- **thyroid hormones**
- **catecholamines**



Thyroxine



Tyrosine

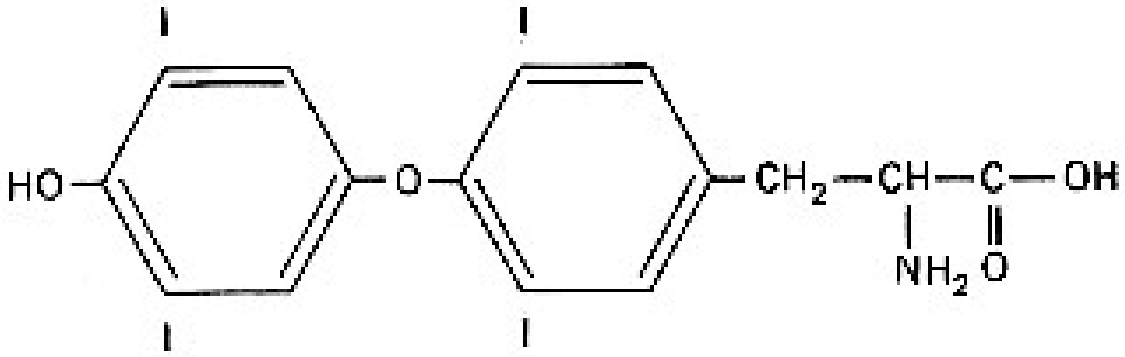


Epinephrine

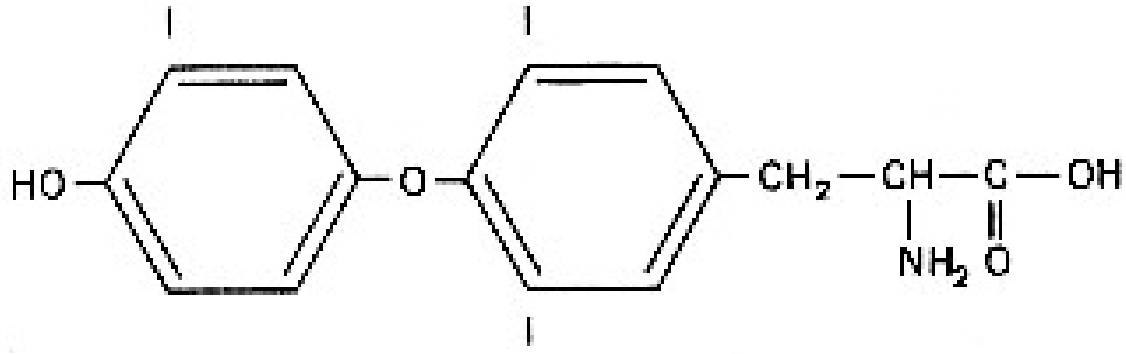
THYROID HORMONE

- Thyroid hormones are basically a "double" tyrosine with the critical incorporation of 3 or 4 iodine atoms
- Thyroid hormone is produced by the thyroid gland and is lipid soluble
- Thyroid hormones are produced by modification of a tyrosine residue contained in thyroglobulin, post-translationally modified to bind iodine, then proteolytically cleaved and released as T4 and T3
- T3 and T4 then bind to thyroxin binding globulin for transport in the blood

THYROID HORMONES



3, 5, 3', 5' – Tetraiodothyronine (thyroxine, T_4)



3, 5, 3'-Triiodothyronine (T_3)

CATECHOLAMINE HORMONES

- Catecholamines are both neurohormones and neurotransmitters.
- These include epinephrine, and norepinephrine
- Epinephrine and norepinephrine are produced by the adrenal medulla both are water soluble
- Secreted like peptide hormones

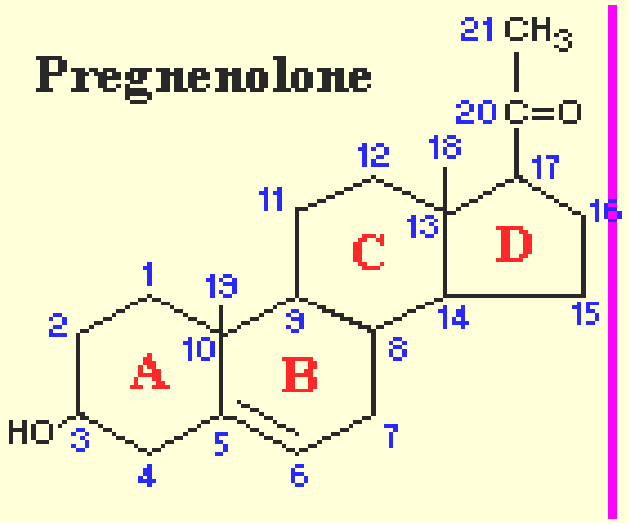
AMINE HORMONES

Two other amino acids are used for synthesis of hormones:

- Tryptophan is the precursor to serotonin and the pineal hormone melatonin
- Histidine is converted to histamine

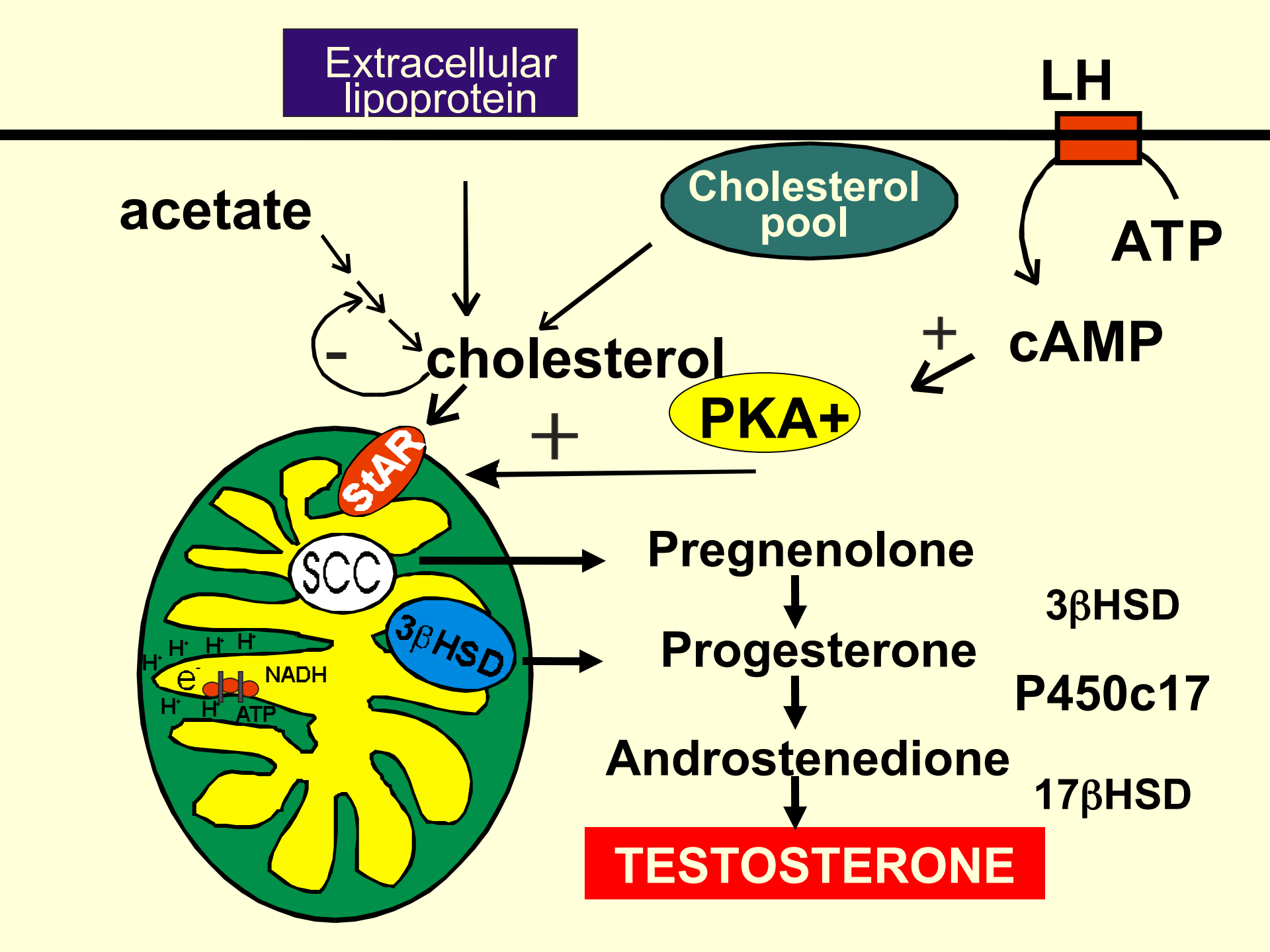
STEROID HORMONES

- All steroid hormones are derived from cholesterol and differ only in the ring structure and side chains attached to it.
- All steroid hormones are lipid soluble.
- Steroid hormones are secreted by the gonads, adrenal cortex, and placenta.



TYPES OF STEROID HORMONES

- Glucocorticoids - cortisol is the major representative in most mammals
- Mineralocorticoids - aldosterone being most prominent
- Androgens - such as testosterone
- Estrogens - including estradiol and estrone
- Progestogens - such as progesterone (also known a progestins)


Extracellular lipoprotein
LH
ATP
acetate
Cholesterol pool
cAMP
+
-
cholesterol
PKA+
+
StAR
SCC
3βHSD
H+ H+ H+ H+
e-
NADH
H+ H+
ATP
Pregnenolone
3βHSD
Progesterone
P450c17
Androstenedione
17βHSD
TESTOSTERONE

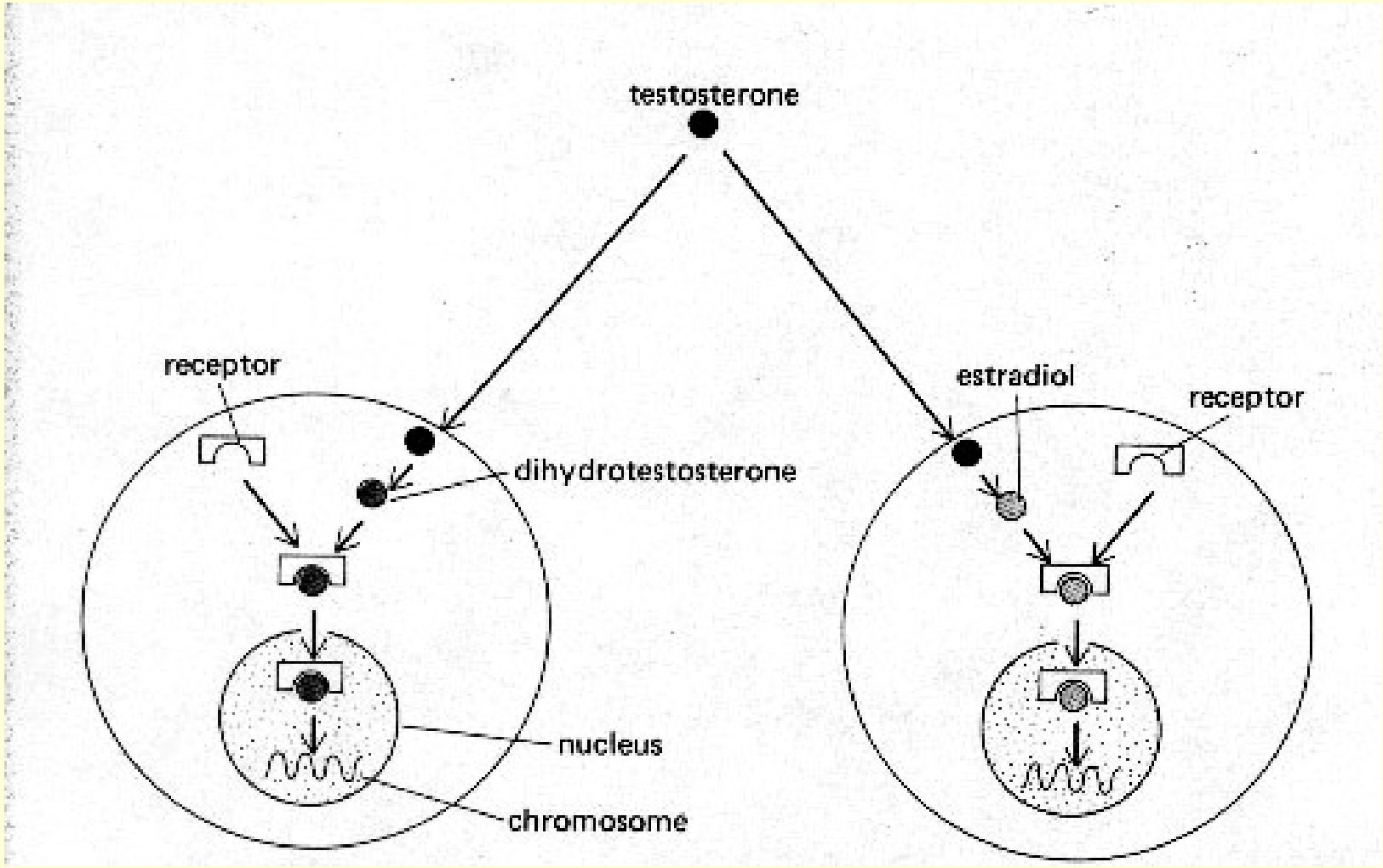
STEROID HORMONES

- Are not packaged, but synthesized and immediately released
- Enzymes which produce steroid hormones from cholesterol are located in mitochondria and smooth ER
- Steroids are lipid soluble and thus are freely permeable to membranes so are not stored in cells

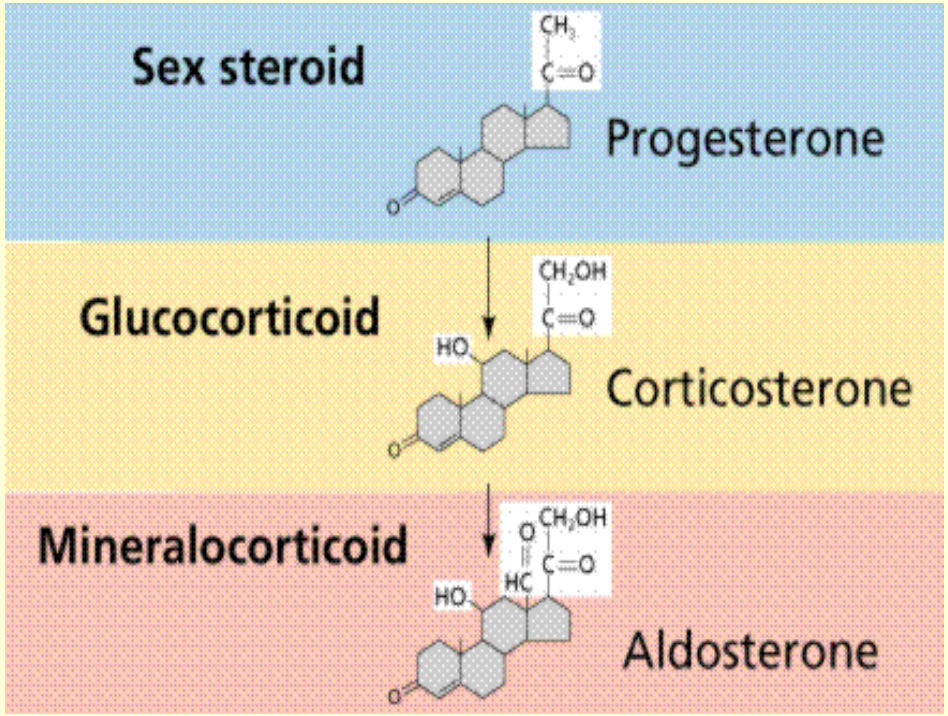
STEROID HORMONES

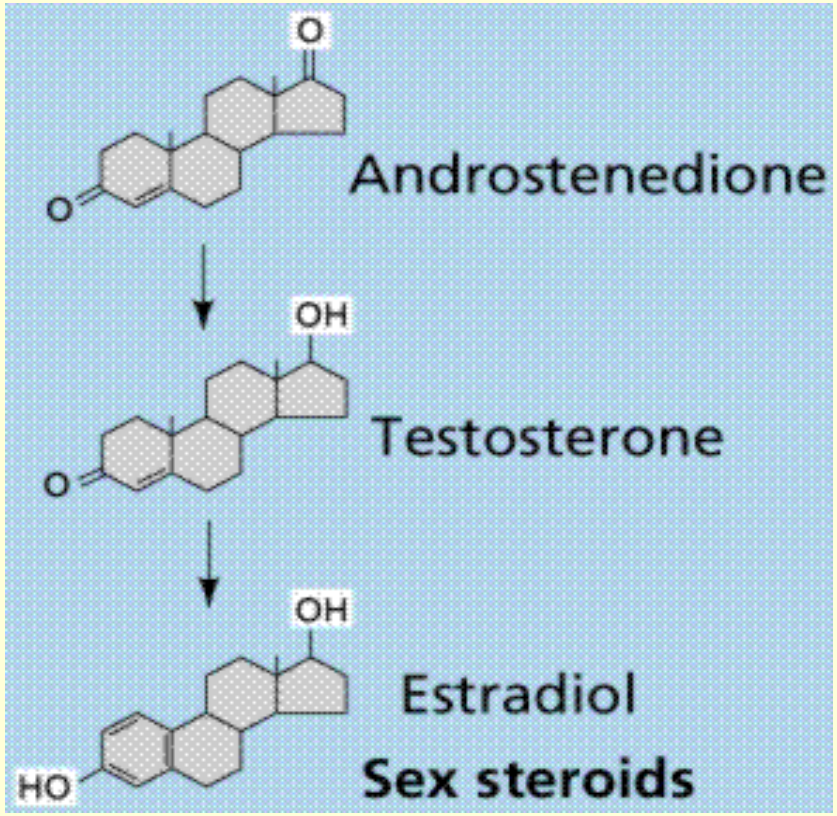
- Steroid hormones are not water soluble so have to be carried in the blood complexed to specific binding globulins
- Corticosteroid binding globulin carries cortisol
- Sex steroid binding globulin carries testosterone and estradiol
- In some cases a steroid is secreted by one cell and is converted to the active steroid by the target cell (androgen - which secreted by the gonad and converted into estrogen in the brain)

STEROIDS CAN BE TRANSFORMED TO ACTIVE STEROID IN TARGET CELL



STRUCTURE OF SOME STEROID HORMONES AND PATHWAYS OF THEIR FORMATION

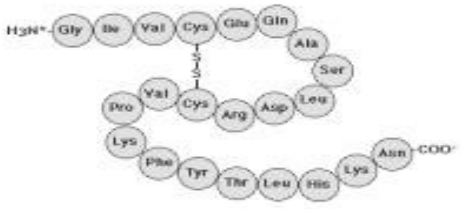




HORMONES ARE GROUPED INTO CLASSES BASED ON THEIR STRUCTURE

Peptides | **Amines** | **Steroids**

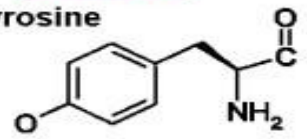
Peptides



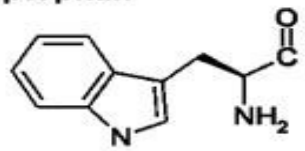
- **MOST** hormones are of this variety

Amines

Tyrosine



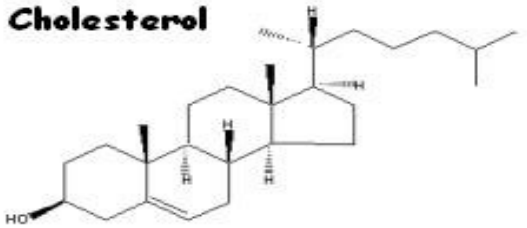
Tryptophan



- Thyroid
  - Triiodothyronine (T3)
  - Thyroxine (T4)
- Adrenal medulla
  - Epinephrine
- Pineal gland
  - Melatonin

Steroids

Cholesterol



- Adrenal cortex
  - Aldosterone
  - Cortisol
- Gonads
  - Testosterone
  - Estrogen
  - Progesterone
  - others...

Regardless of their structure, all hormones act through RECEPTORS

CONTROL OF ENDOCRINE ACTIVITY

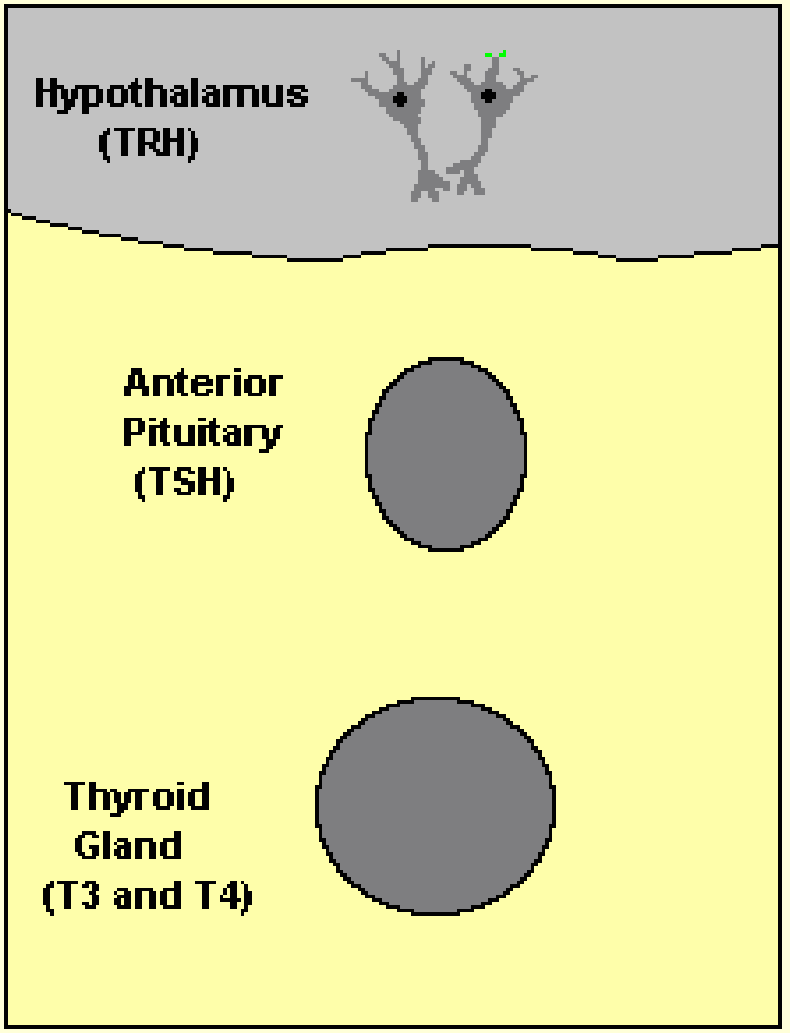
- The physiologic effects of hormones depend largely on their concentration in blood and extracellular fluid
- The concentration of hormone as seen by target cells is determined by three factors:
  - Rate of production
  - Rate of delivery
  - Rate of degradation and elimination

CONTROL OF ENDOCRINE ACTIVITY

- **Rate of production: Synthesis and secretion of hormones are the most highly regulated aspect of endocrine control. Such control is mediated by positive and negative feedback circuits**
- **Rate of delivery: An example of this effect is blood flow to a target organ or group of target cells - high blood flow delivers more hormone than low blood flow**
- **Rate of degradation and elimination: Hormones, like all biomolecules, have characteristic rates of decay, and are metabolized and excreted from the body through several routes**

FEEDBACK CONTROL OF HORMONE PRODUCTION

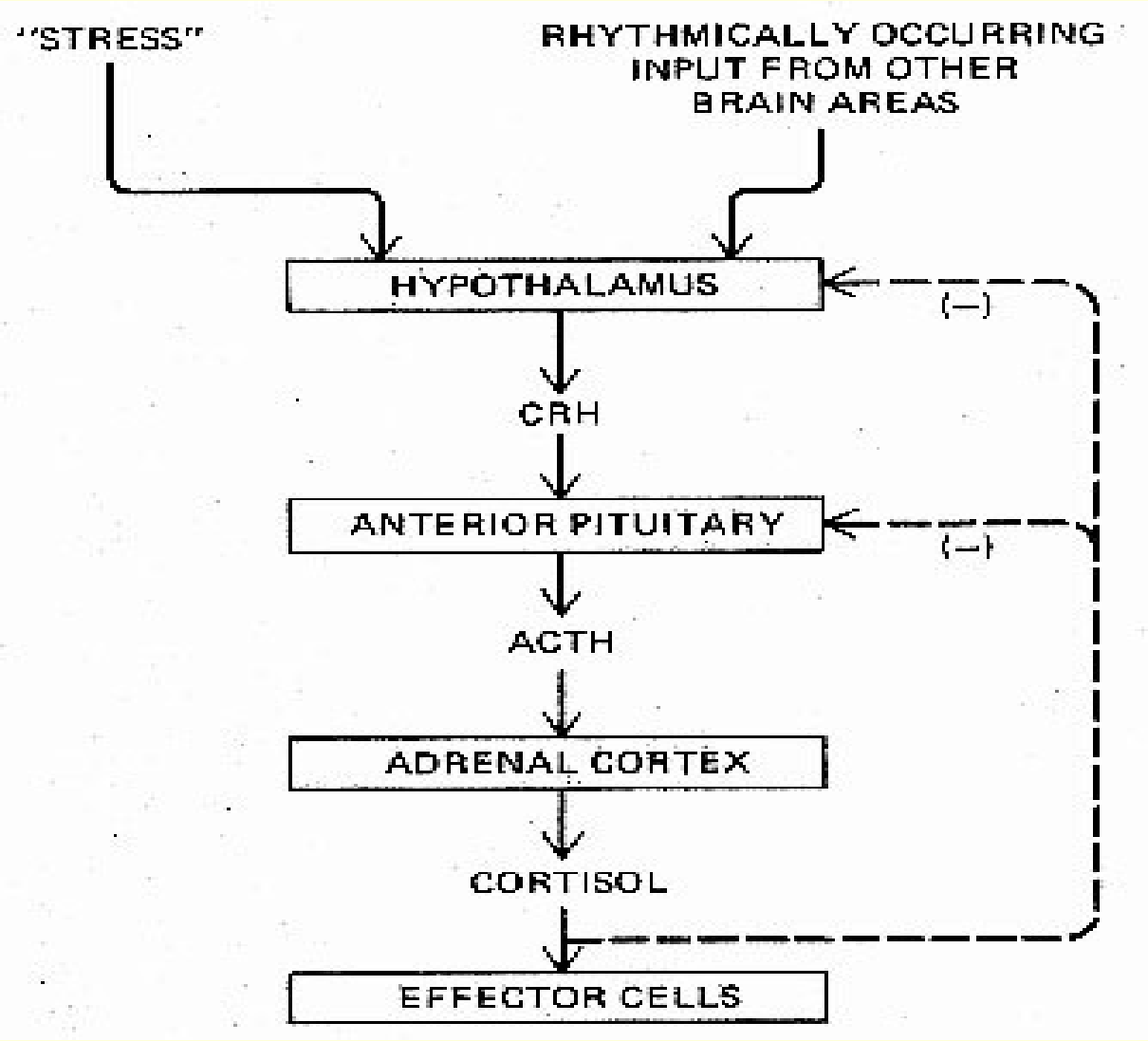
- Feedback loops are used extensively to regulate secretion of hormones in the hypothalamic-pituitary axis.
- An important example of a negative feedback loop is seen in control of thyroid hormone secretion



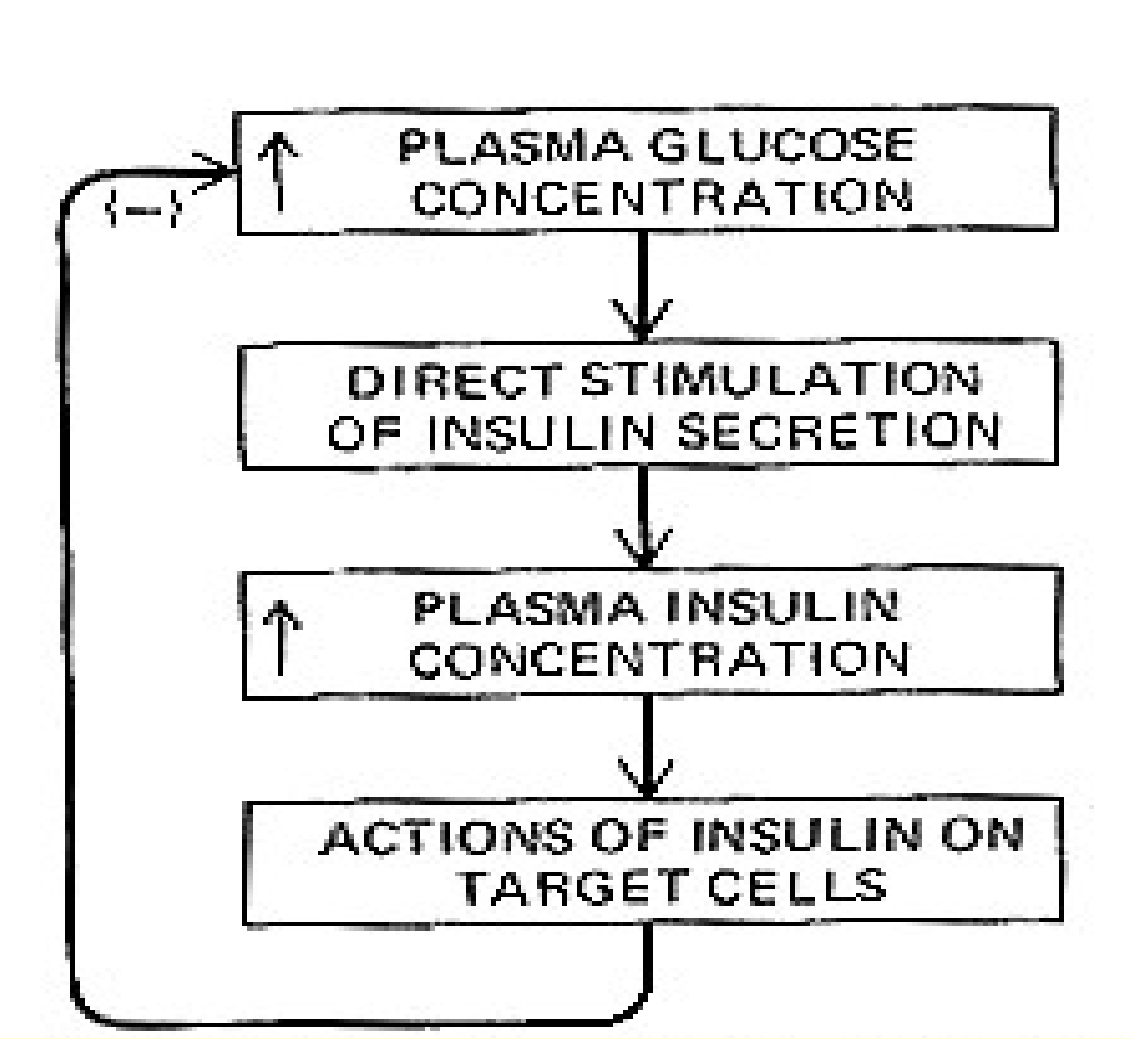
FEEDBACK CONTROL

- **Negative feedback is most common: for example, LH from pituitary stimulates the testis to produce testosterone which in turn feeds back and inhibits LH secretion**
- **Positive feedback is less common: examples include LH stimulation of estrogen which stimulates LH surge at ovulation**

NEGATIVE FEEDBACK EFFECTS OF CORTISOL

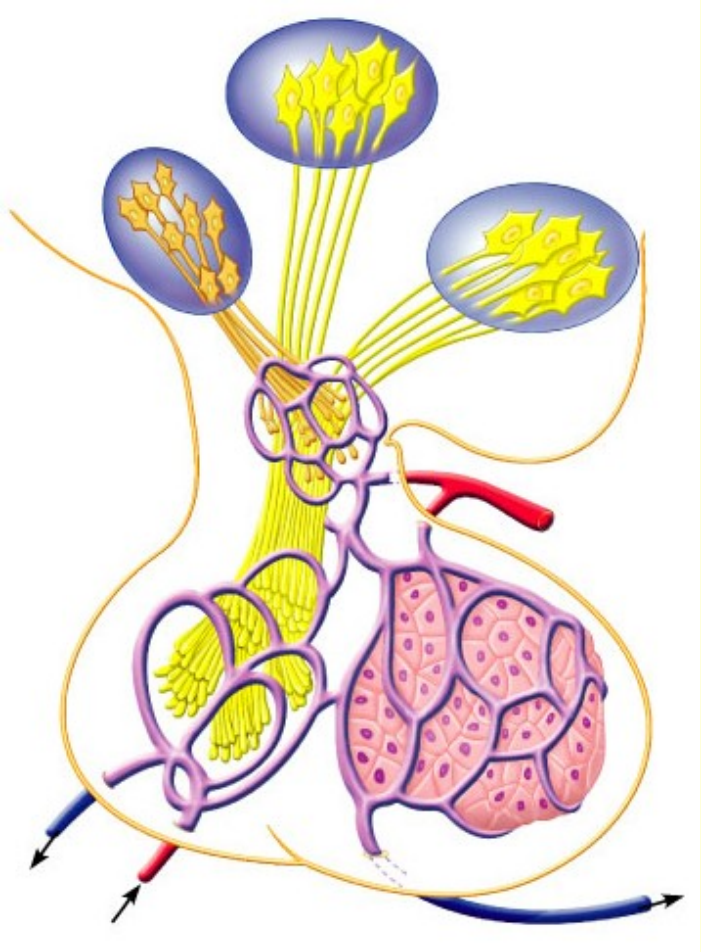


FEEDBACK CONTROL OF INSULIN BY GLUCOSE CONCENTRATIONS



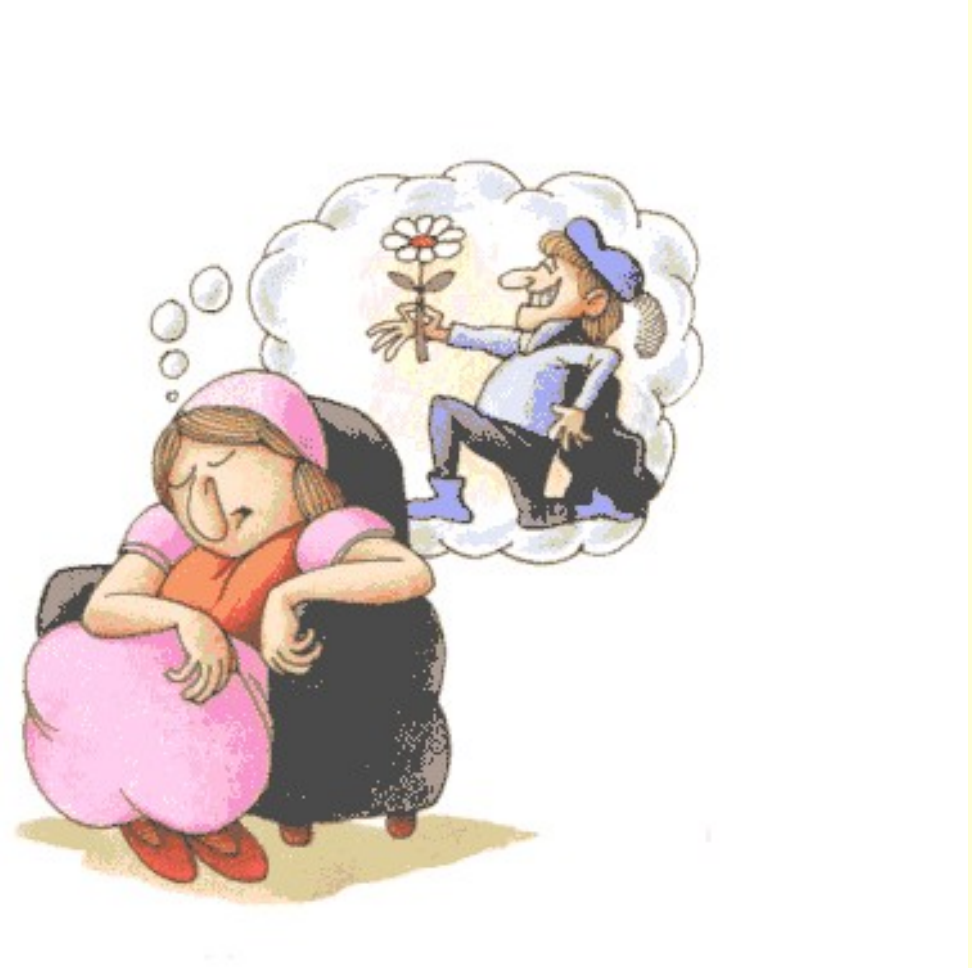
NEURAL CONTROL OF HORMONE PRODUCTION

- Neural input to hypothalamus stimulates synthesis and secretion of releasing factors which stimulate pituitary hormone production and release



CHRONOTROPIC CONTROL OF HORMONE PRODUCTION

- endogenous neuronal rhythmicity
- diurnal rhythms, circadian rhythms (growth hormone and cortisol)
- sleep-wake cycle
- seasonal rhythm

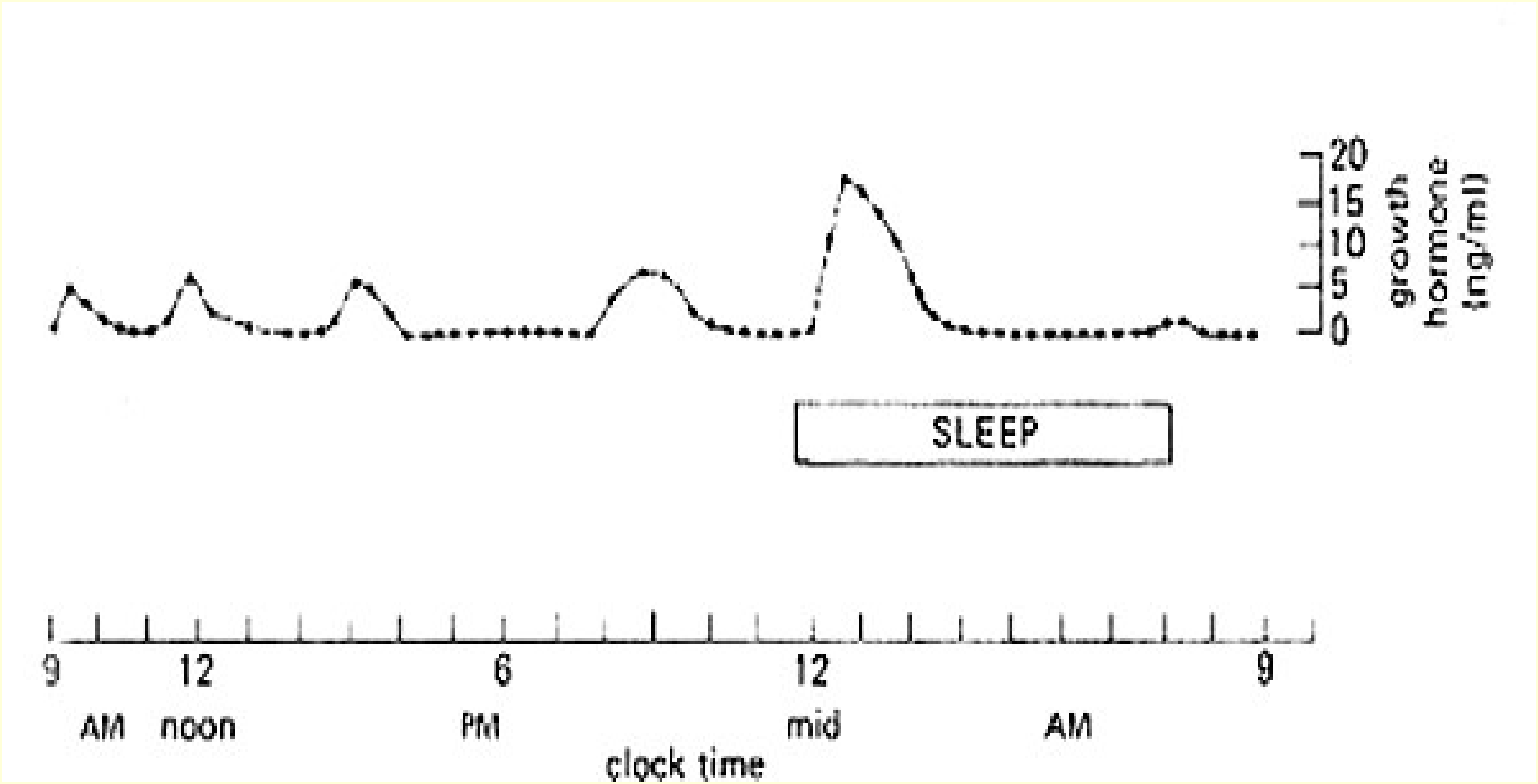


EPISODIC SECRETION OF HORMONES

Secretory episodes occur with different periodicity:

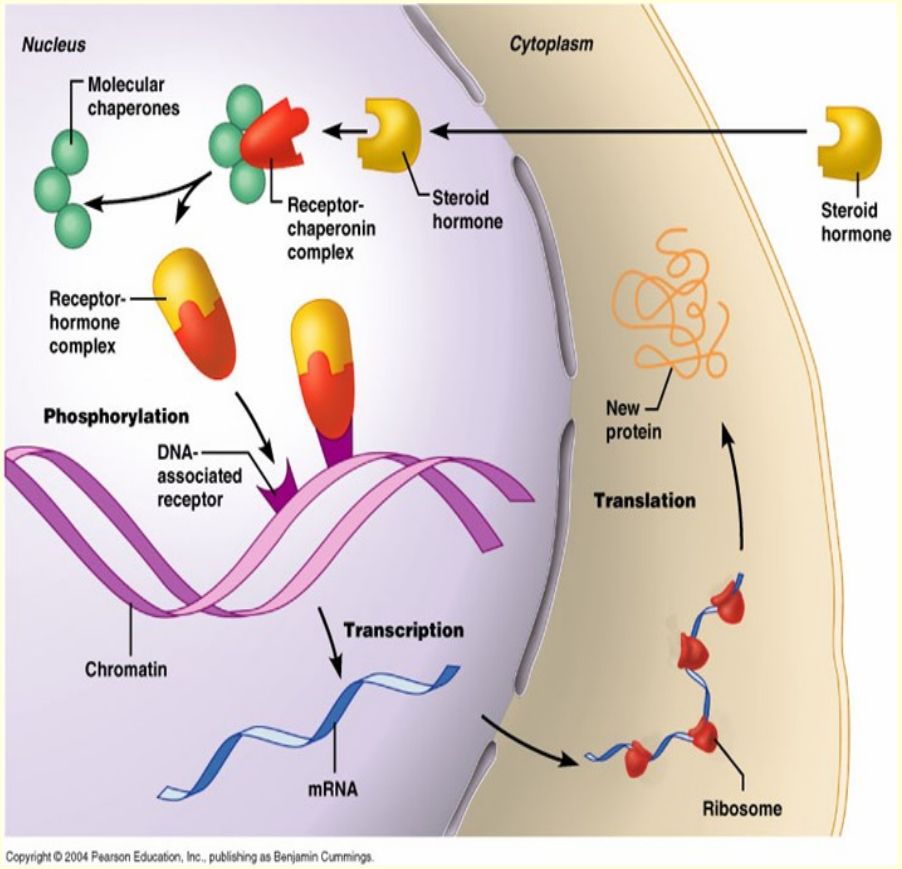
- **pulses can be as frequent as every 5-10 minutes**
- **the most prominent episodes of release occur with a frequency of about one hour - referred to as *circhoral***
- **an episode of release longer than an hour, but less than 24 hours - the rhythm is referred to as *ultradian***
- **if the periodicity is approximately 24 hours - the rhythm is referred to as *circadian***

Circadian (chronotropic) control



HORMONE-RECEPTOR INTERACTIONS

- **Definition: a protein that binds a ligand with high affinity and low capacity. This binding must be saturuable.**
- **A tissue becomes a target by expressing a specific receptor for it (only cells with receptors for hormone are targets for its action).**



AGONIST - ANTAGONIST

- **Agonists are molecules that bind the receptor and induce all the post-receptor events that lead to a biologic effect. In other words, they act like the "normal" hormone, although perhaps more or less potently**
- **Antagonists are molecules that bind the receptor and block binding of the agonist, but fail to trigger intracellular signaling events**

SPARE RECEPTORS

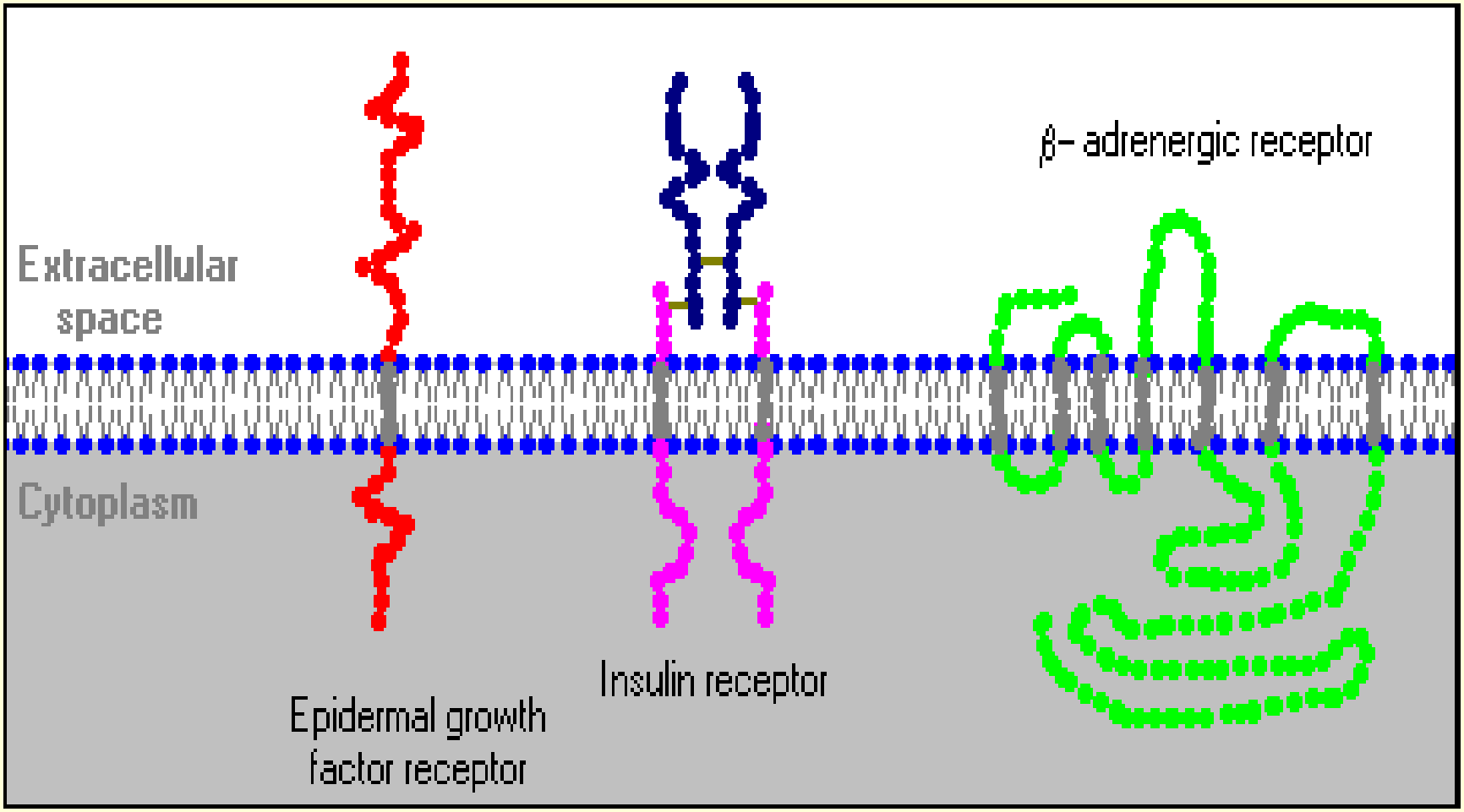
- In most systems the maximum biological response is achieved at concentrations of hormone lower than required to occupy all of the receptors on the cell
- Examples:
  - insulin stimulates maximum glucose oxidation in adipocytes with only 2-3% of receptors bound
  - LH stimulates maximum testosterone production in Leydig cells when only 1% of receptors are bound

TYPES OF RECEPTORS

- Receptors for the water soluble hormones are found on the surface of the target cell, on the plasma membrane.
- These types of receptors are coupled to various second messenger systems which mediate the action of the hormone in the target cell.
- Receptors for the lipid soluble hormones reside in the nucleus (and sometimes the cytoplasm) of the target cell.

  - Because these hormones can diffuse through the lipid bilayer of the plasma membrane, their receptors are located on the interior of the target cell

VARIATIONS IN RECEPTOR STRUCTURE

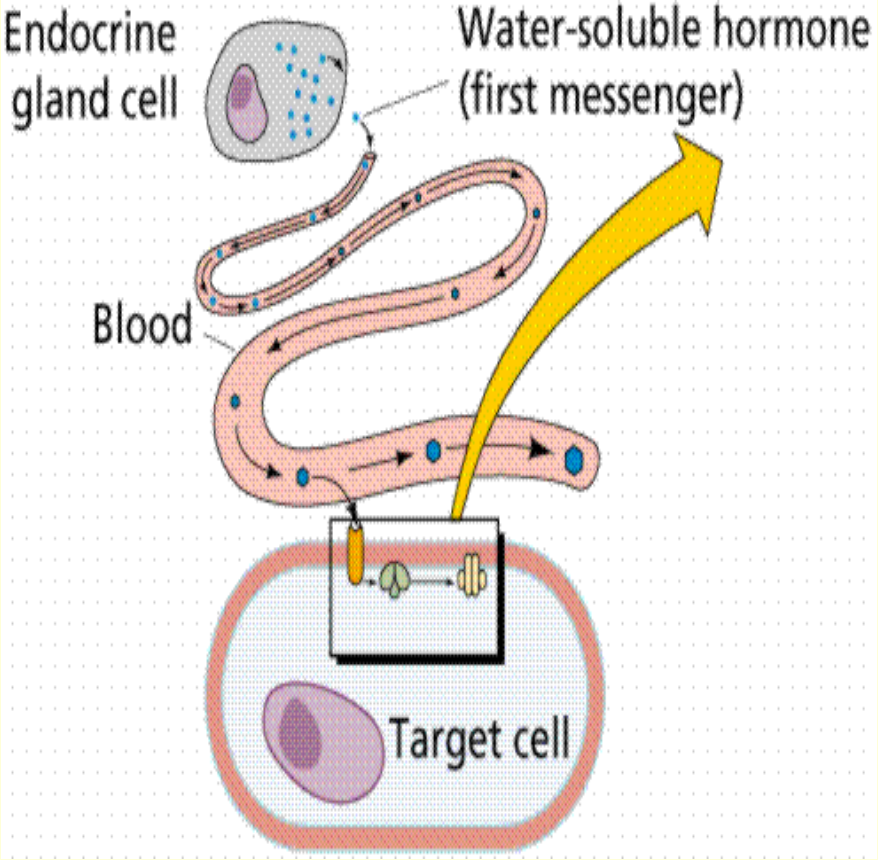


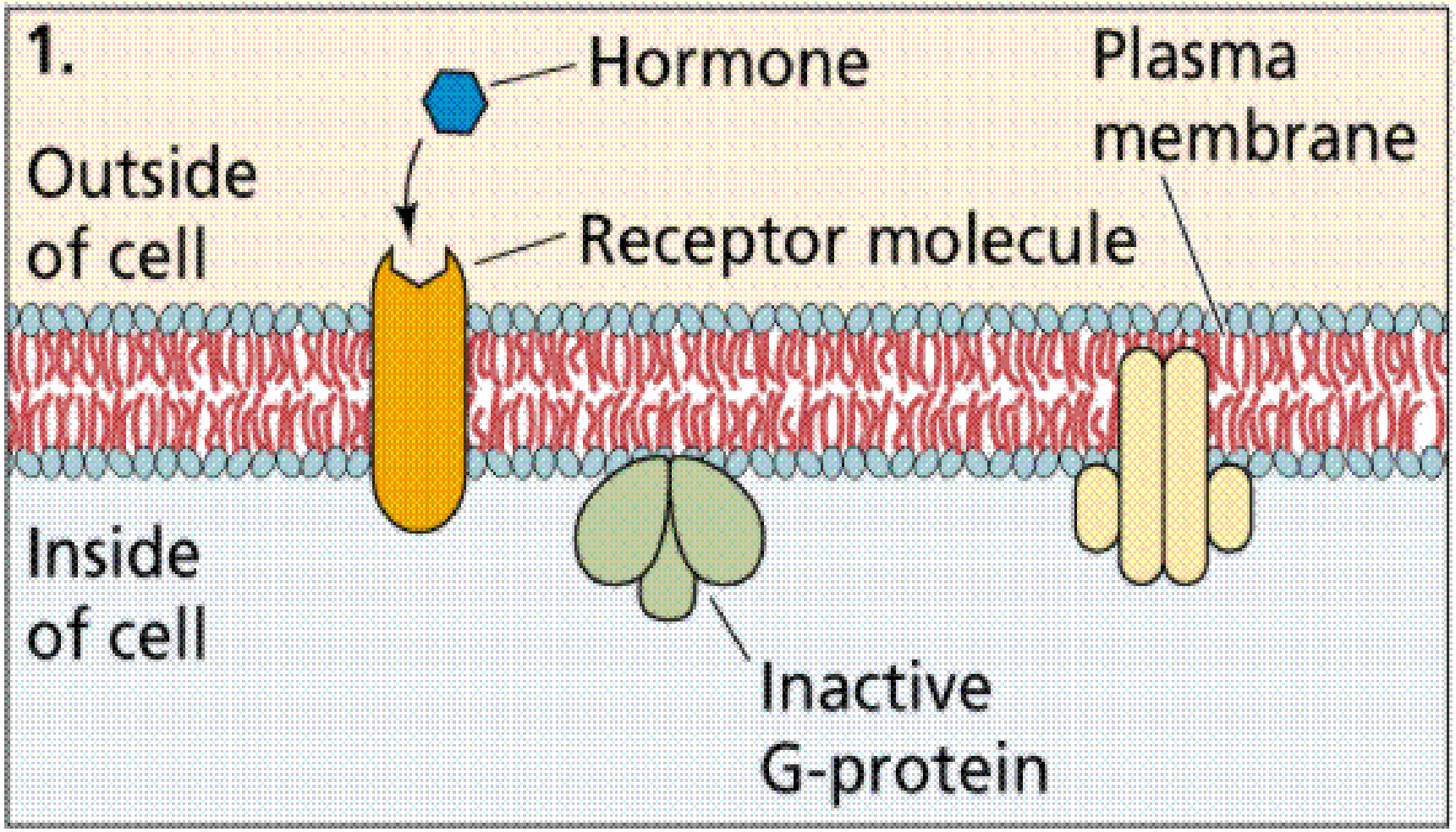
SECOND MESSENGER SYSTEMS

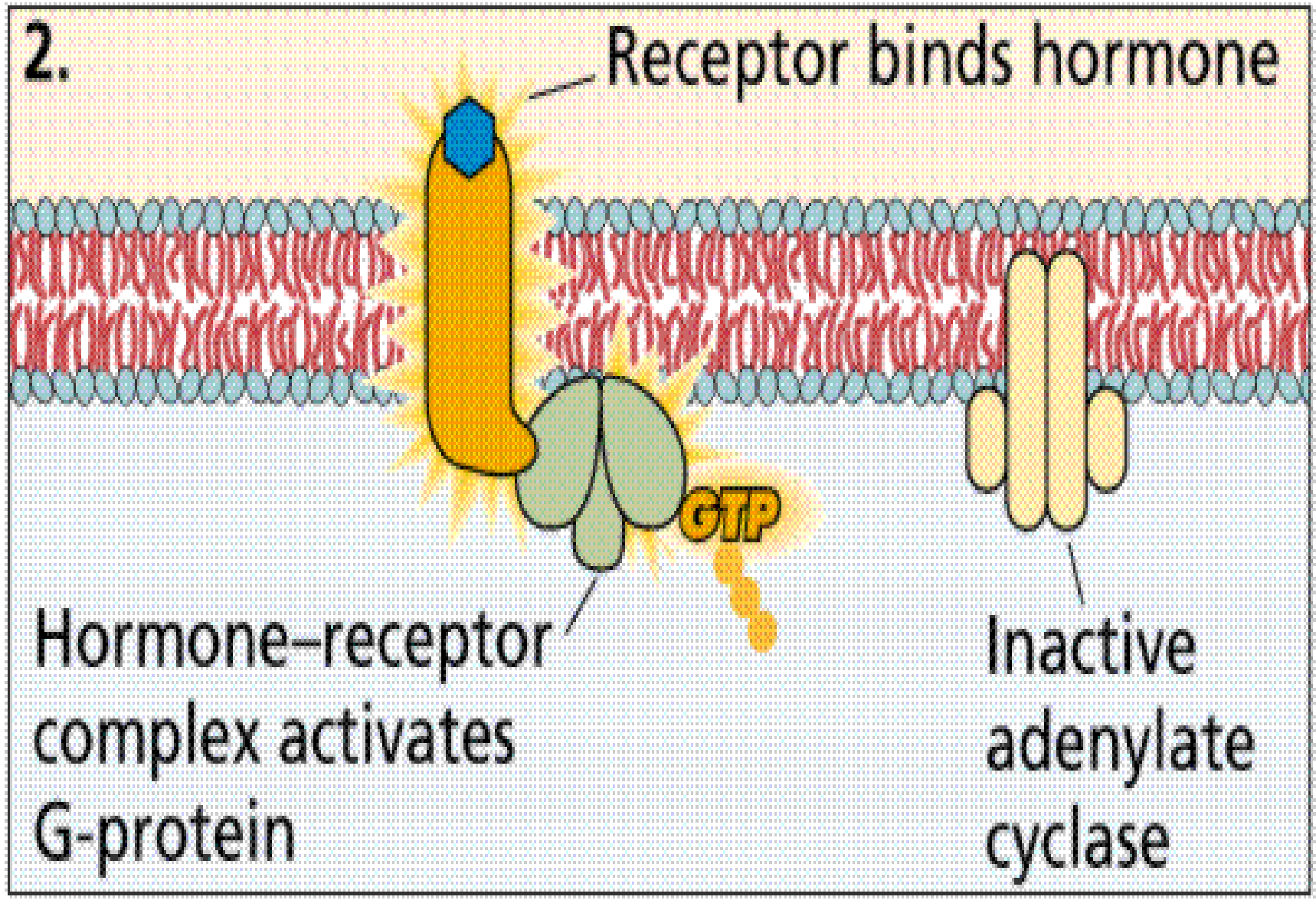
- Each of these second messenger systems activates a specific protein kinase enzyme.
- These include cyclic nucleotide-dependent protein kinases
- Calcium/calmodulin-dependent protein kinase, and protein kinase C which depends on diacyl glycerol binding for activation.
- Protein kinase C activity is further increased by calcium which is released by the action of inositol phosphates.

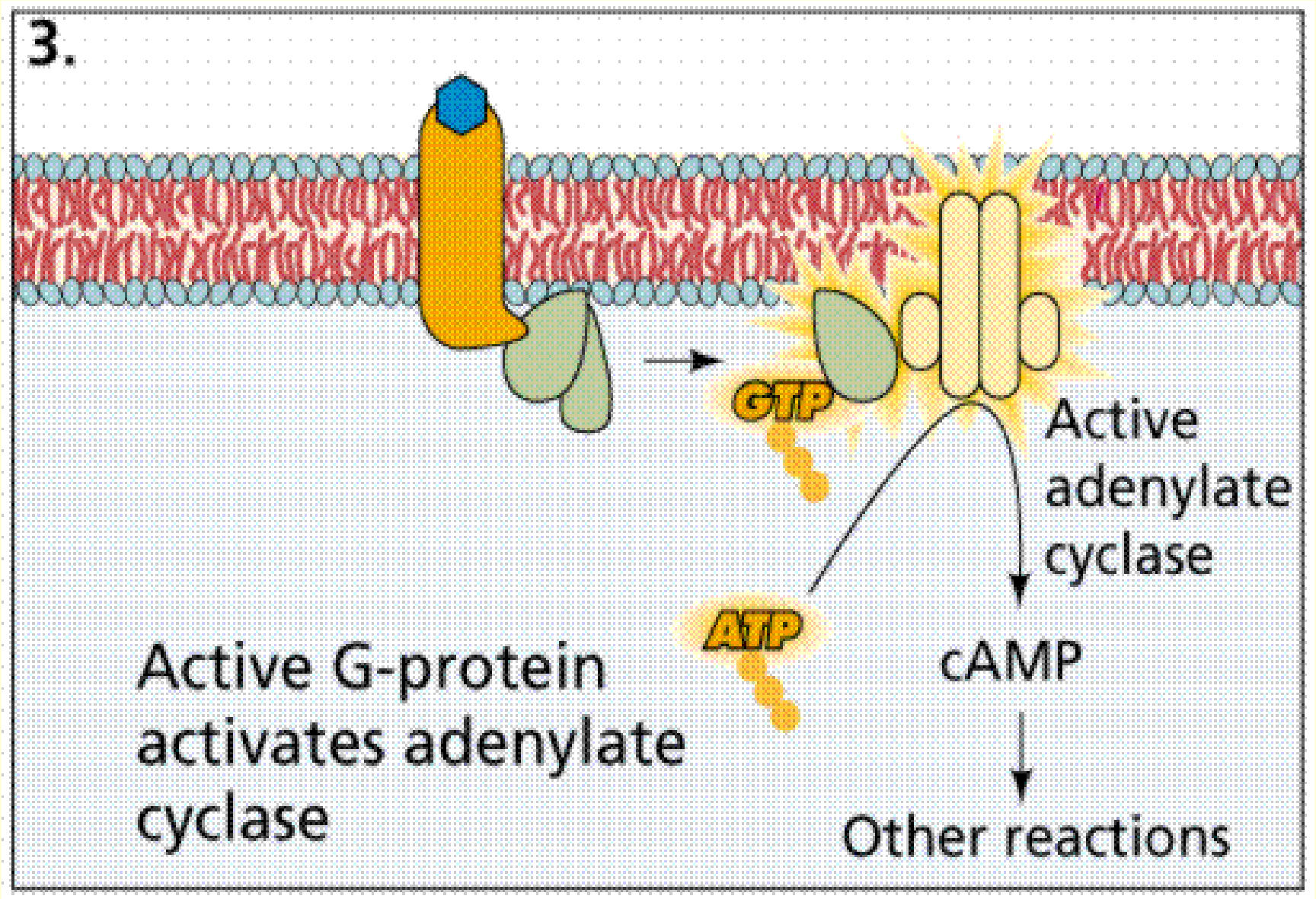
SECOND MESSENGER SYSTEMS

- The generation of second messengers and activation of specific protein kinases results in changes in the activity of the target cell which characterizes the response that the hormone evokes
- Changes evoked by the actions of second messengers are usually rapid




1.
Hormone
Plasma membrane
Outside of cell
Receptor molecule
Inside of cell
Inactive G-protein


2.
Receptor binds hormone
GTP
Hormone–receptor complex activates G-protein
Inactive adenylate cyclase

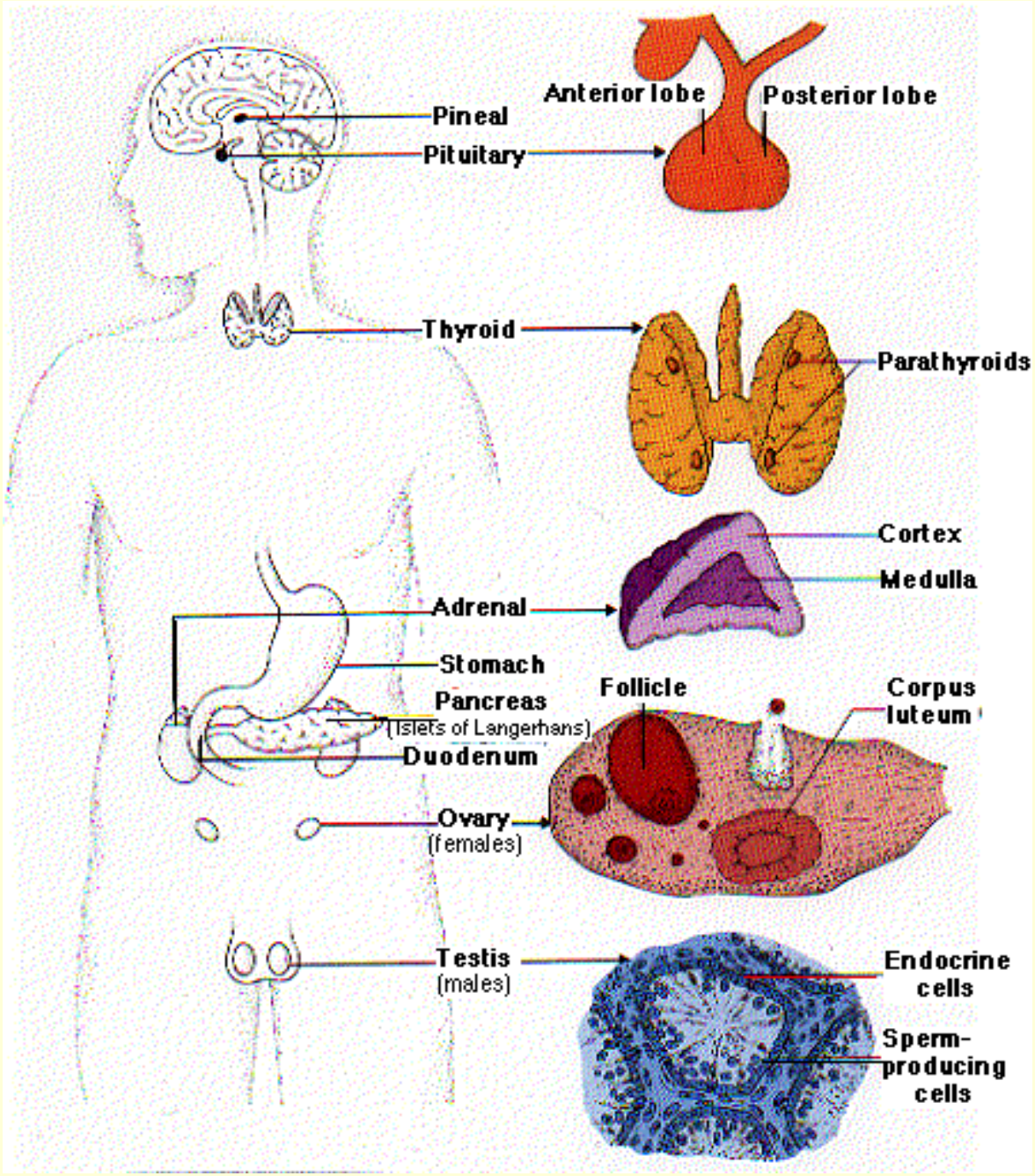

3.
GTP
Active
adenylate
cyclase
ATP
cAMP
Active G-protein
activates adenylate
cyclase
Other reactions

RECEPTOR CONTROL MECHANISMS

- **Hormonally induced negative regulation of receptors is referred to as *homologous-desensitization***
- **This homeostatic mechanism protects from toxic effects of hormone excess**
- ***Heterologous desensitization* occurs when exposure of the cell to one agonist reduces the responsiveness of the cell any other agonist that acts through a different receptor**
- **This most commonly occurs through receptors that act through the adenylyl cyclase system**
- **Heterologous desensitization results in a broad pattern of refractoriness with slower onset than homologous desensitization**

Endocrine-related Problems

- Overproduction of a hormone
- Underproduction of a hormone
- Nonfunctional receptors that cause target cells to become insensitive to hormones


Pineal
Pituitary
Anterior lobe
Posterior lobe
Thyroid
Parathyroids
Cortex
Medulla
Adrenal
Stomach
Pancreas
(Islets of Langerhans)
Duodenum
Follicle
Corpus luteum
Ovary
(females)
Testis
(males)
Endocrine cells
Sperm-producing cells

ENDOCRINE GLANDS FUNCTIONS

- **Hypothalamus - activates and controls the part of the nervous system that controls involuntary body functions, the hormonal system, and many body functions, such as regulating sleep and stimulating appetite.**
- **Pituitary gland - produces a number of different hormones that influence various other endocrine glands.**
- **Pineal body - involved with daily biological cycles.**

ENDOCRINE GLANDS FUNCTIONS

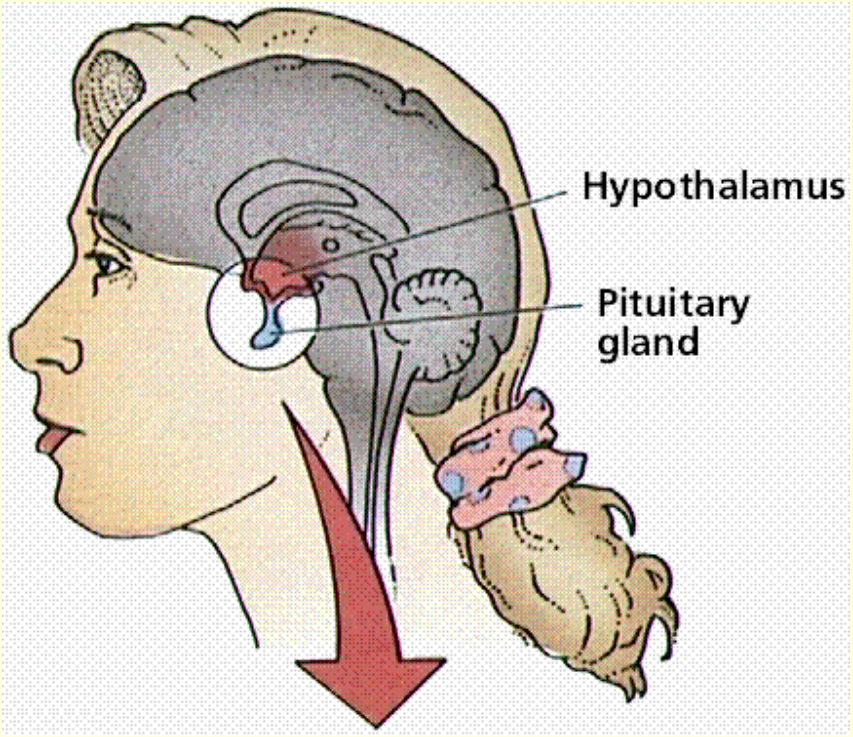
- Thymus gland - plays a role in the body's immune system.
- Thyroid gland - produces hormones that stimulate body heat production, bone growth, and the body's metabolism.
- Parathyroid glands - secrete a hormone that maintains the calcium level in the blood.

ENDOCRINE GLANDS FUNCTIONS

- Adrenal glands - divided into 2 regions; secrete hormones that influence the body's metabolism, blood chemicals, and body characteristics, as well as influence the part of the nervous system that is involved in the response and defense against stress.
- Pancreas - secrete hormones (insulin and glucagon) that control the use of glucose by the body.
- Ovaries and testicles - secrete hormones that influence female and male characteristics, respectively.

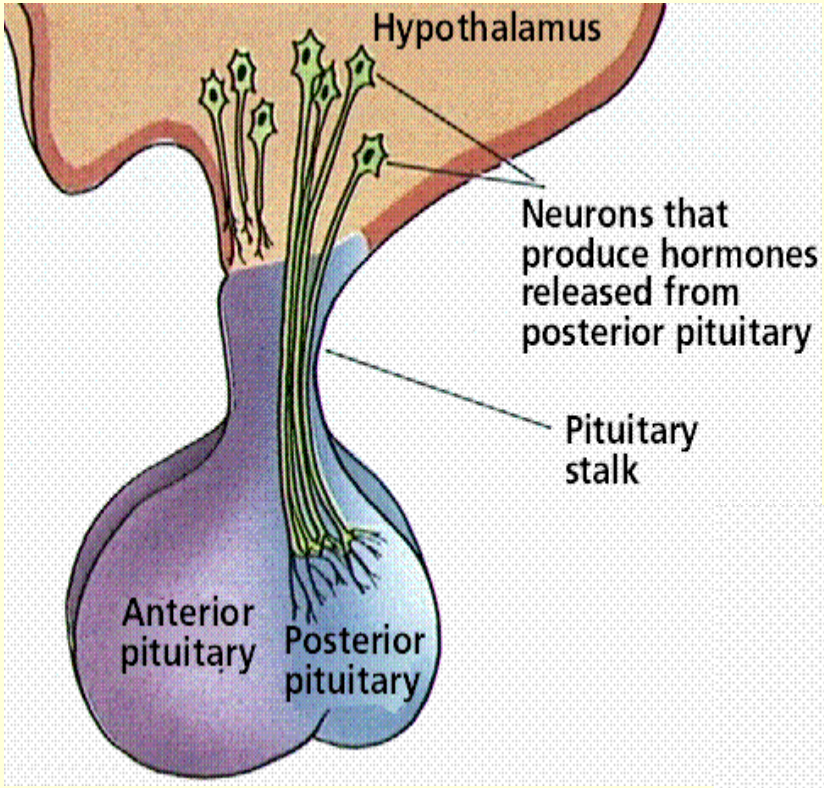
Hypothalamus and Pituitary

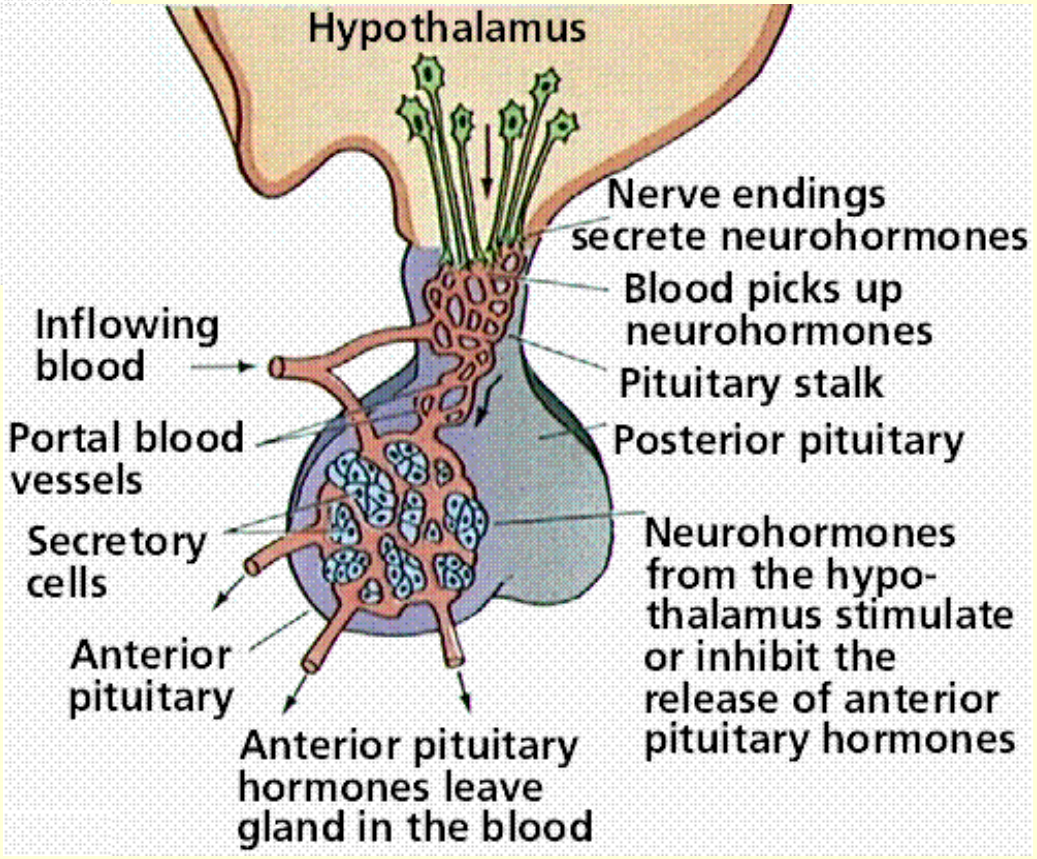
THE NERVOUS AND ENDOCRINE SYSTEMS



- There is a stalk links the pituitary to the hypothalamus, which controls release of pituitary hormones
- The hypothalamus contains neurons that control releases from the anterior pituitary.
- Seven hypothalamic hormones are released into a portal system connecting the hypothalamus and pituitary, and cause targets in the pituitary to release eight hormones

The location and roles of the hypothalamus and pituitary glands





Hypothalamus and Pituitary

- The hypothalamus-pituitary unit is the most dominant portion of the entire endocrine system.
- The output of the hypothalamus-pituitary unit regulates the function of the thyroid, adrenal and reproductive glands and also controls somatic growth, lactation, milk secretion and water metabolism.

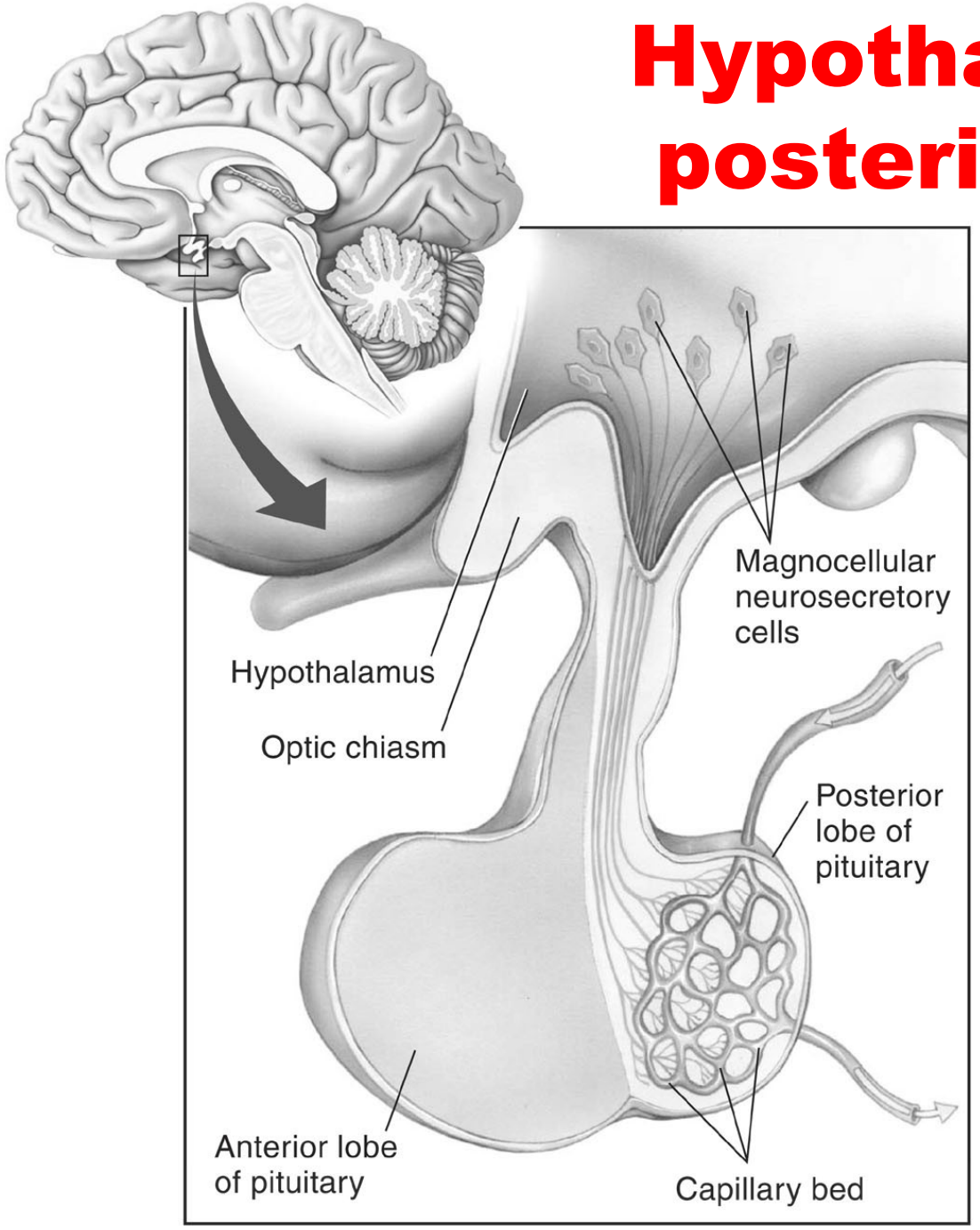
Hypothalamus and Pituitary

- Pituitary function depends on the hypothalamus and the anatomical organization of the hypothalamus-pituitary unit reflects this relationship.
- The pituitary gland lies in a pocket of bone at the base of the brain, just below the hypothalamus to which it is connected by a stalk containing nerve fibers and blood vessels. The pituitary is composed to two lobes - anterior and posterior

POSTERIOR PITUITARY: NEUROHYPOPHYSIS

- Posterior pituitary: an outgrowth of the hypothalamus composed of neural tissue.
- Hypothalamic neurons pass through the neural stalk and end in the posterior pituitary.
- The upper portion of the neural stalk extends into the hypothalamus and is called the median eminence.

Hypothalamus and posterior pituitary

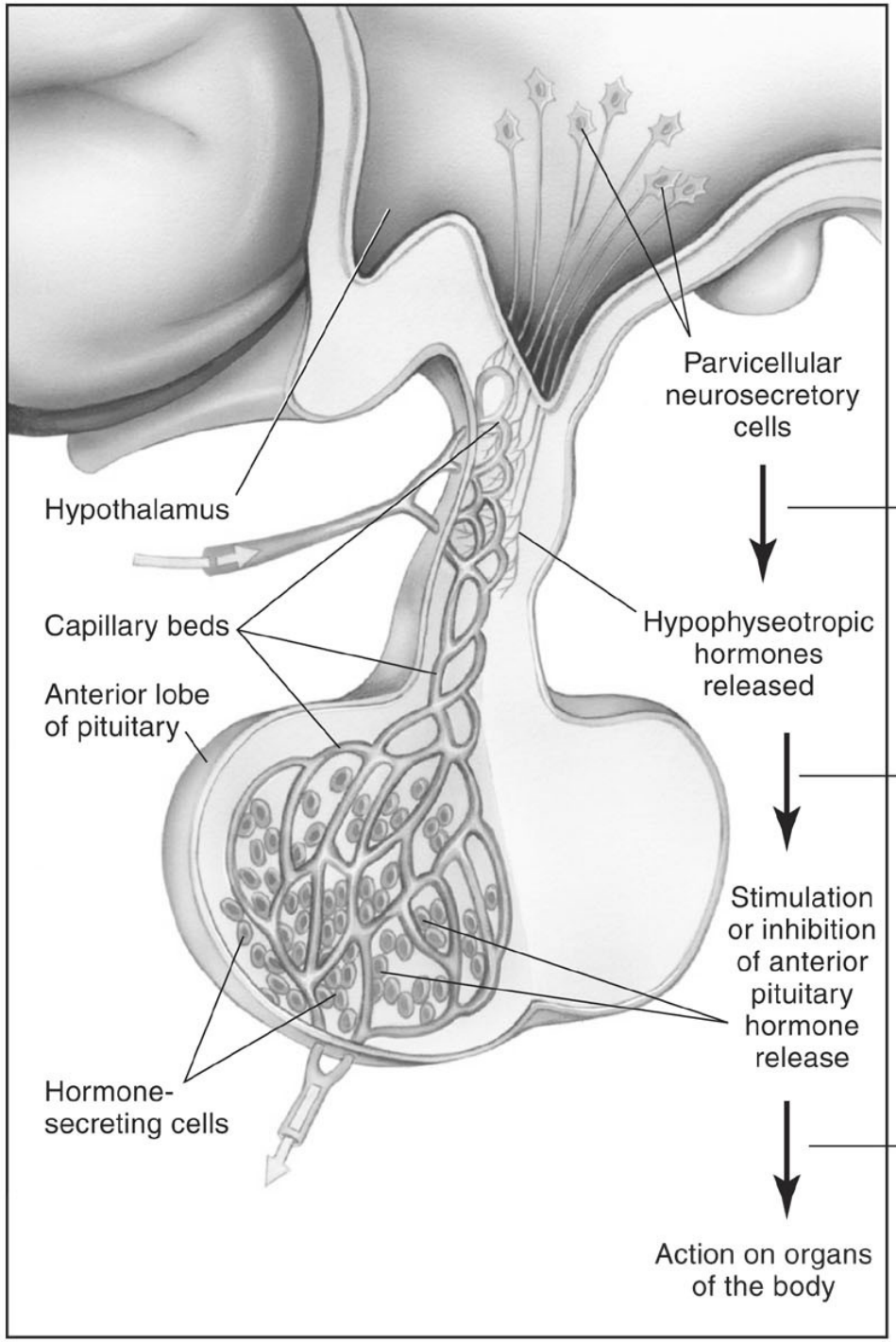


Midsagital view illustrates that magnocellular neurons paraventricular and supraoptic nuclei secrete oxytocin and vasopressin directly into capillaries in the posterior lobe

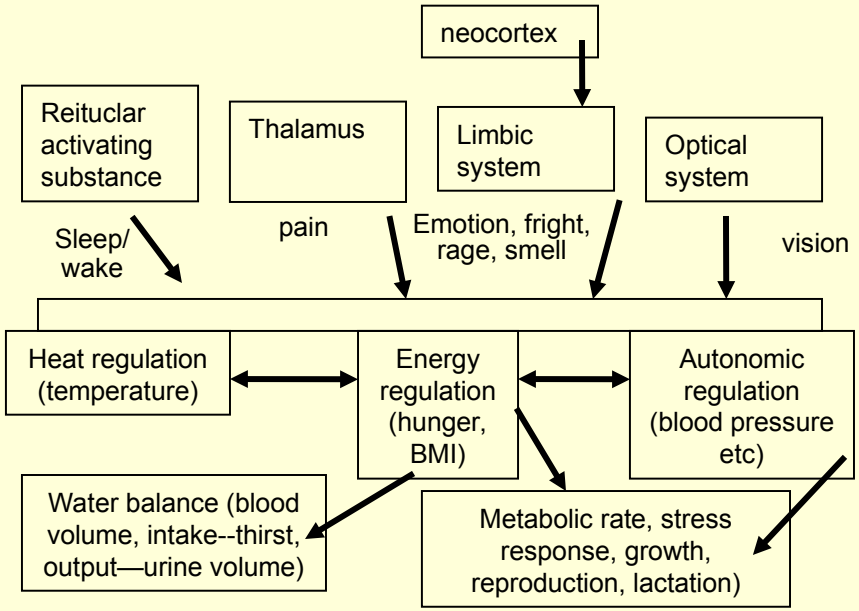
Anterior pituitary: adenohypophysis

- Anterior pituitary: connected to the hypothalamus by the superior hypophyseal artery.
- The anterior pituitary is an amalgam of hormone producing glandular cells.
- The anterior pituitary produces six peptide hormones: prolactin, growth hormone (GH), thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH).

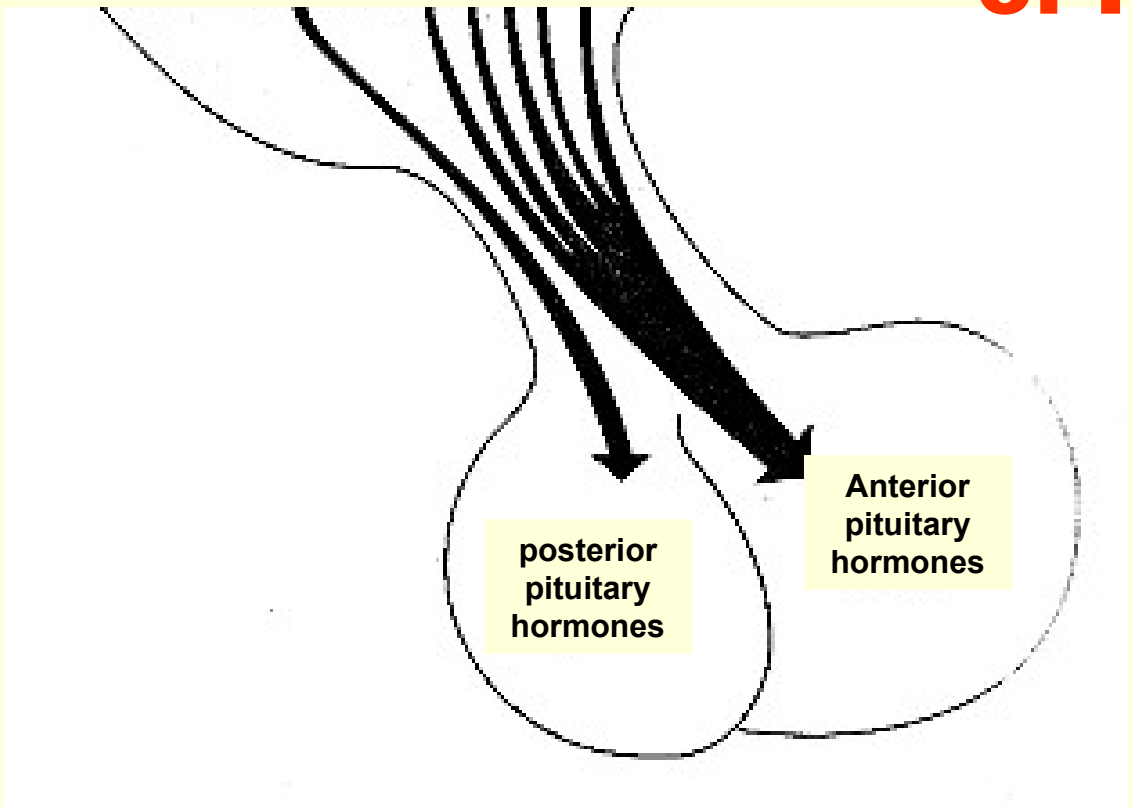
Hypothalamus and anterior pituitary



Midsagital view illustrates parvicellular neurosecretory cells secrete releasing factors into capillaries of the pituitary portal system at the median eminence which are then transported to the anterior pituitary gland to regulate the secretion of pituitary hormones.



Regulation of Hypothalamus



Hypothalamic releasing factors for anterior pituitary hormones

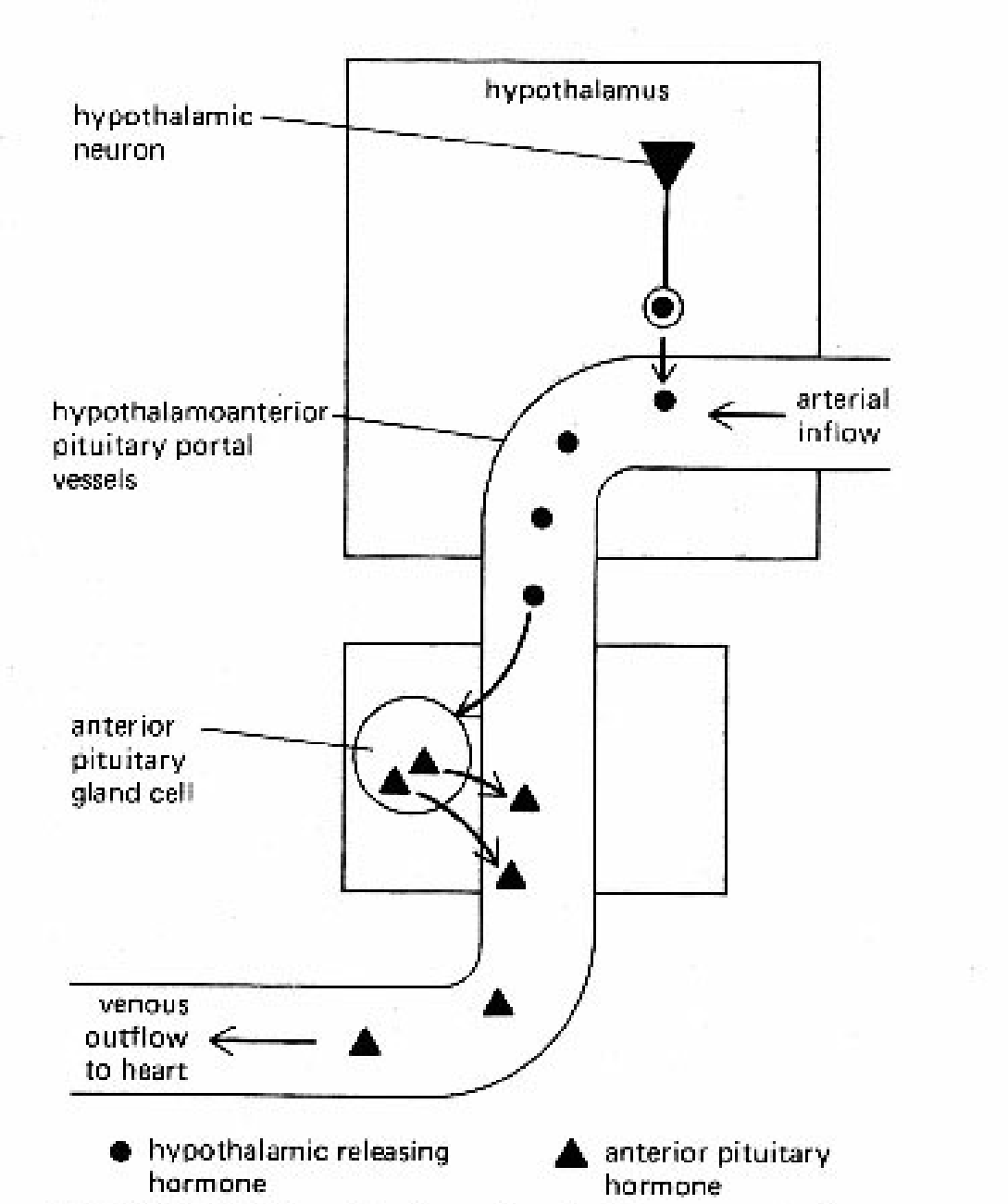
- Travel to adenohypophysis via hypophyseal-portal circulation
- Travel to specific cells in anterior pituitary to stimulate synthesis and secretion of trophic hormones

Hypothalamic releasing hormones

Hypothalamic releasing hormone	Effect on pituitary
Corticotropin releasing hormone (CRH)	Stimulates ACTH secretion
Thyrotropin releasing hormone (TRH)	Stimulates TSH and Prolactin secretion
Growth hormone releasing hormone (GHRH)	Stimulates GH secretion
Somatostatin	Inhibits GH (and other hormone) secretion
Gonadotropin releasing hormone (GnRH) a.k.a LHRH	Stimulates LH and FSH secretion
Prolactin releasing hormone (PRH)	Stimulates PRL secretion
Prolactin inhibiting hormone (dopamine)	Inhibits PRL secretion

Characteristics of hypothalamic releasing hormones

- Secretion in pulses
- Act on specific membrane receptors
- Transduce signals via second messengers
- Stimulate release of stored pituitary hormones
- Stimulate synthesis of pituitary hormones
- Stimulates hyperplasia and hypertophy of target cells
- Regulates its own receptor



Hypothalamus and anterior pituitary

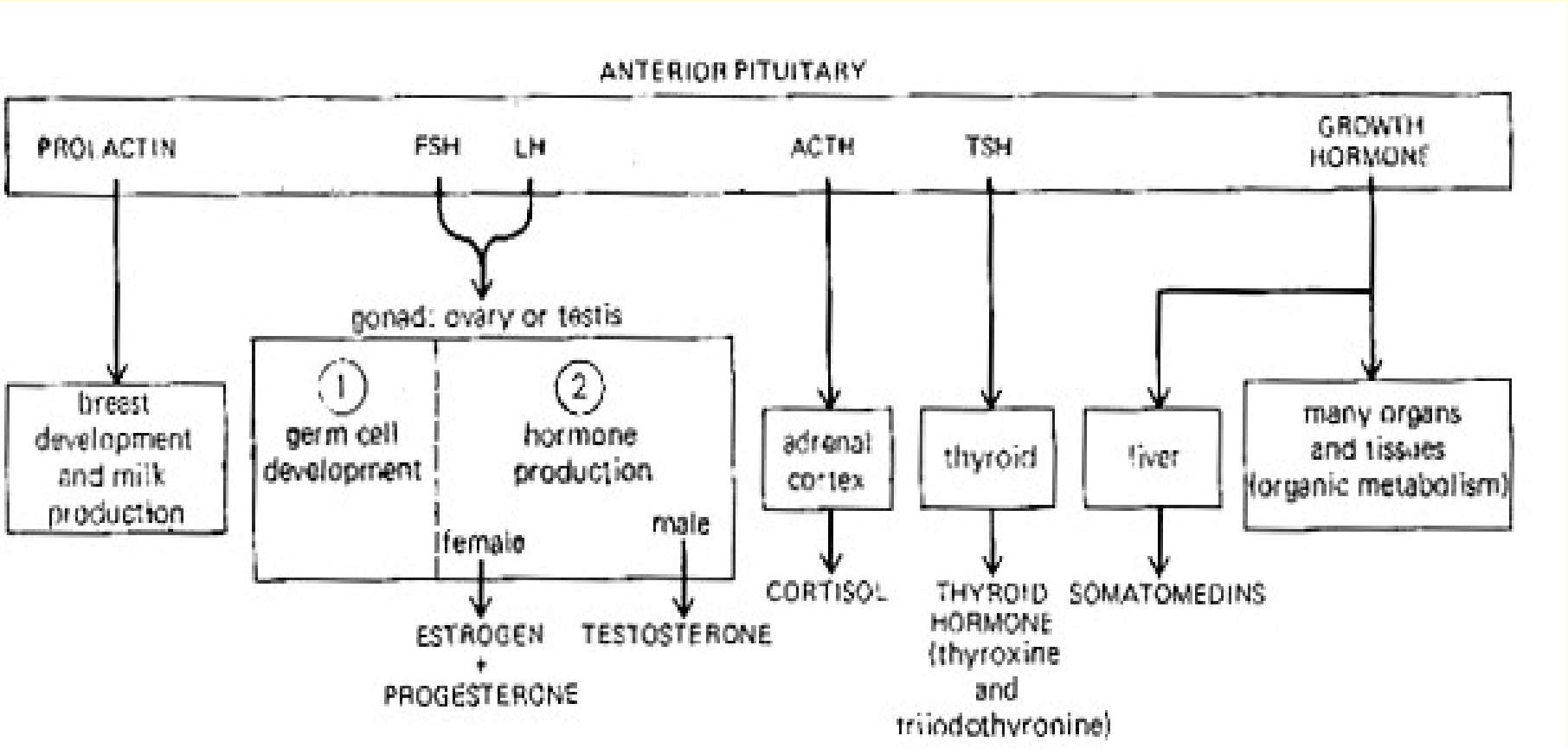
Anterior pituitary

- Anterior pituitary: connected to the hypothalamus by hypothalmoanterior pituitary portal vessels.
- The anterior pituitary produces six peptide hormones:
  - prolactin
  - growth hormone (GH)
  - thyroid stimulating hormone (TSH)
  - adrenocorticotropic hormone (ACTH)
  - follicle-stimulating hormone (FSH)
  - luteinizing hormone (LH)

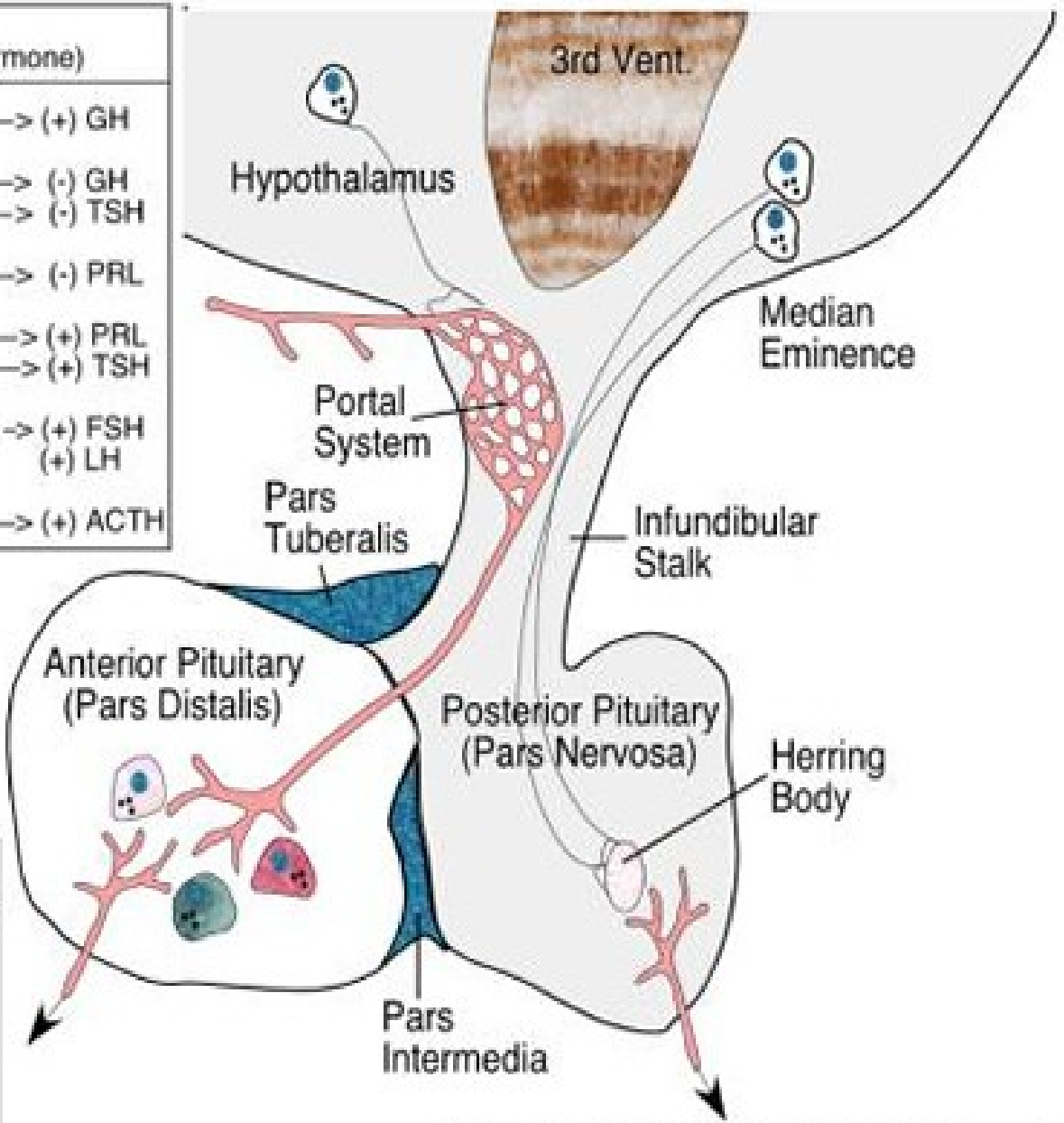
Anterior pituitary cells and hormones

Cell type	Pituitary population	Product	Target
Corticotroph	15-20%	ACTH beta-lipotropin	Adrenal gland Adipocytes Melanocytes
Thyrotroph	3-5%	TSH	Thyroid gland
Gonadotroph	10-15%	LH, FSH	Gonads
Somatotroph	40-50%	GH	All tissues, liver

Anterior pituitary hormones

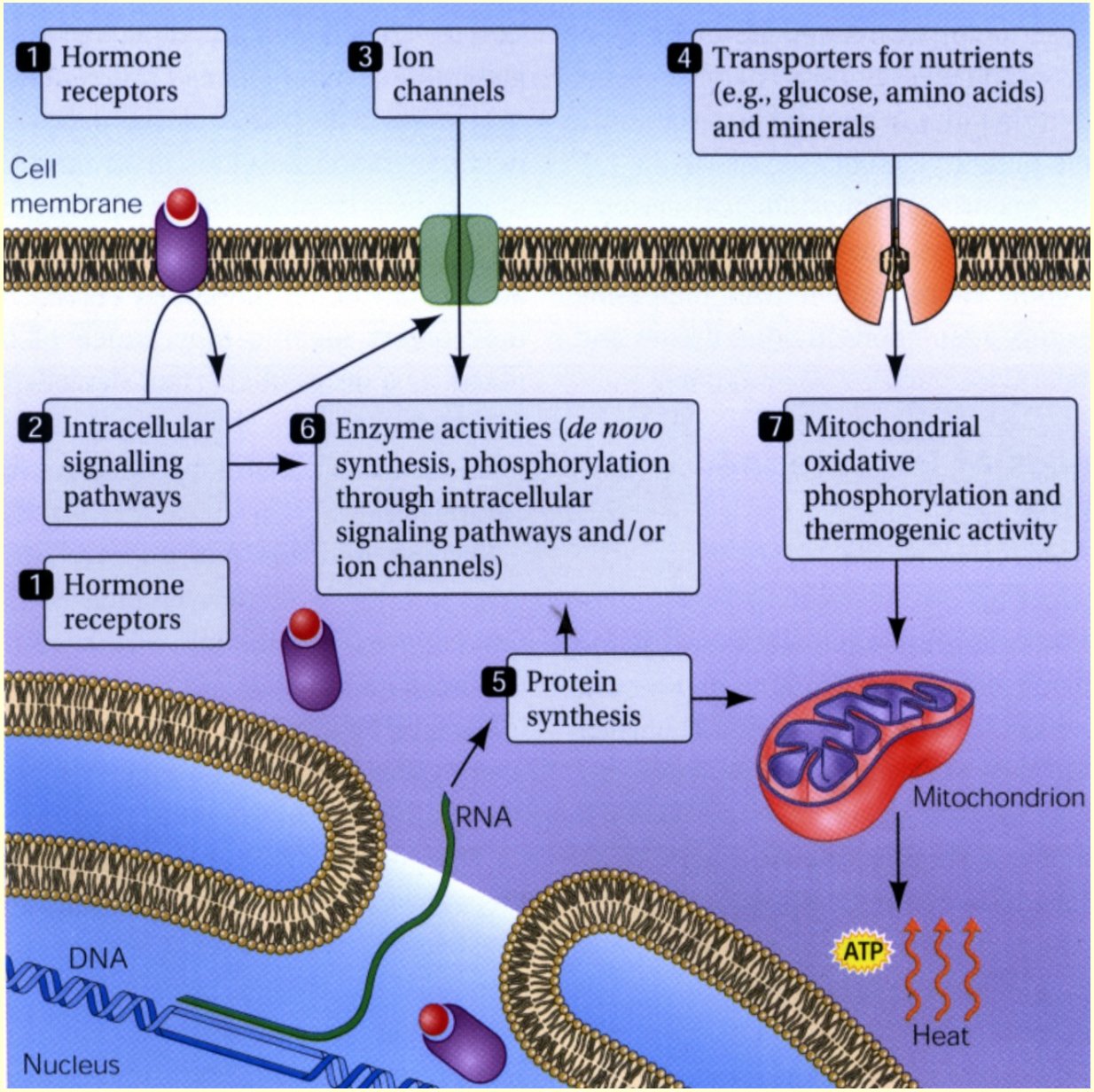


Hypothalamic Factors: Hormone	Target Cell (hormone)	
GH releasing Hormone (GHRH)	> Somatotrope	—> (+) GH
Somatostatin (SRIF)	—> Somatotrope	—> (-) GH
	—> Thyrotrope	—> (-) TSH
Dopamine	—> Lactotrope	—> (-) PRL
Thyrotropin releasing hormone (TRH)	-> Lactotrope	—> (+) PRL
	—> Thyrotrope	—> (+) TSH
Gonadotropin releasing hormone (GnRH)	> Gonadotropes	-> (+) FSH (+) LH
Corticotropin Rel. Horm. (CRH)	-> Corticotrope	—> (+) ACTH



Hormones released into blood: Cell type	Hormone
Acidophils	
Somatotropes (45%)	Growth Hormone (GH)
Lactotropes (25%)	Prolactin (PRL)
Basophils	
Thyrotropes (5%)	Thyrotropin (TSH)
Gonadotropes (5%)	Follitropin (FSH) or Luteotropin (LH)
Corticotropes (20%)	Corticotropin (ACTH) Melanocyte Stim. Hormone (MSH)

Hormones released at nerve terminals: Hormone	Target tissues:
Vasopressin (ADH)	Kidney, vasculature
Oxytocin	Mammary gland, uterus



I thank all of you for your patience!